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<p>(21) International Application Number: PCT/SE98/00587</p> <p>(22) International Filing Date: 30 March 1998 (30.03.98)</p> <p>(30) Priority Data: 9701219-9 4 April 1997 (04.04.97) SE</p> <p>(71) Applicant (for all designated States except US): ASTRA PHARMACEUTICALS LTD. [GB/GB]; Home Park, Kings Langley, Herts. WD4 8DH (GB).</p> <p>(71) Applicant (for MG only): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): KINDON, Nicholas [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). MEGHANI, Premji [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). THOM, Stephen [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB).</p> <p>(74) Agent: ASTRA AKTIEBOLAGET; Patent Dept., S-151 85 Södertälje (SE).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>
<p>(54) Title: NOVEL PHOSPHATE COMPOUNDS AND THEIR USE AS MEDICAMENTS</p> <p>(57) Abstract</p> <p>The invention provides novel phosphate derivatives, processes for their preparation, pharmaceutical compositions containing them, and their use in the treatment of inflammatory conditions.</p>		

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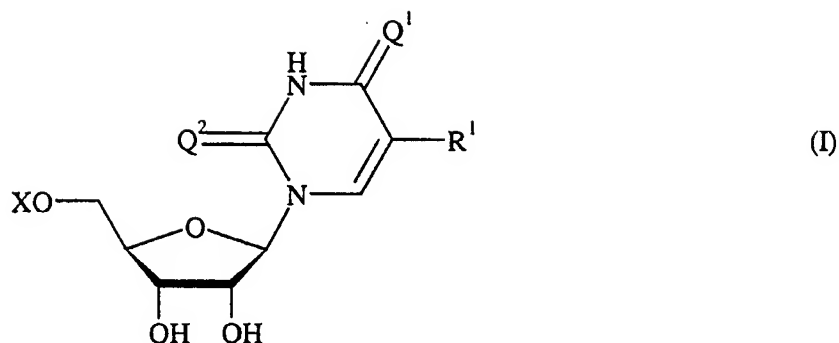
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NOVEL PHOSPHATE COMPOUNDS AND THEIR USE AS MEDICAMENTS

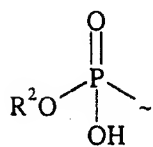
The invention provides new pharmaceutically active compounds, compositions containing them and processes for their preparation. The compounds are useful in therapy because they are P2-purinoceptor 7-transmembrane (TM) G-protein coupled receptor antagonists.

ATP receptors have been shown to be present on a wide number of different cell types (Dubyak *et al* Am J Physiol (1993) 265, C577-C606). Neutrophils, monocytes and macrophages have been isolated from several species including humans and ATP and/or UTP have been shown to increase intracellular calcium levels. Activation of these receptors on leukocytes can either directly stimulate certain types of inflammatory response or can prime the effector cells to other inflammatory mediators *in vivo*. ATP can upregulate the expression of adhesion molecules (Freyer *et al* J Immun. (1988) 141, 580-586) which causes enhanced adhesion of circulating leukocytes to endothelial cells and their enhanced migration into the tissue space. ATP has also been shown to promote chemotaxis of both neutrophils and eosinophils (Verghese *et al* J. B. C. (1996) 271, 15597-15601 and Burders *et al* Blood (1993) 81, 49-55) which may promote an inflammatory response. ATP priming of neutrophils can also potentiate superoxide production (Seifert *et al* Eur J Biochem (1989) 181, 277-285). ATP receptors are also present on a number of other cell types such as chondrocytes, keratinocytes, microglia and goblet cells (Leong *et al* BBA (1994) 1201, 298-304; Pillai *et al* J Clin Invest (1992) 90, 42-51; Walz *et al* J Neuroscience (1993) 13, 4403-4411 and Abdullah *et al* Biochem J (1996) 316, 943-951). Stimulation of the receptors on these cells can stimulate or enhance inflammatory responses and an antagonist of the receptor may therefore be of use in a number of inflammatory diseases such as asthma, inflammatory bowel disease, ARDS, psoriasis, rheumatoid arthritis, myocardial ischaemia, COPD, cystic fibrosis, arteriosclerosis, restenosis, periodontal disease, septic shock, osteoarthritis and stroke. ATP receptors have also been reported on tumour cells (Dubyak *et al* J. Biol. Chem., (1985) 260, 10653 - 10661 and Wagner *et al* Gastroenterology, (1997), 112(4) suppl. page A1198) and may be involved in the development of cancer. Antagonists may therefore be useful in treatment of cancer.

According to the invention there is provided a compound of formula (I) or salts thereof:

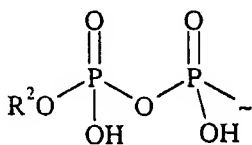


wherein X represents H or a group of formula (i), (ii) or (iii):

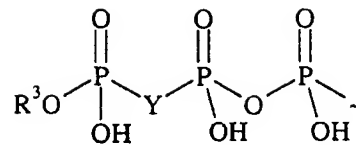


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(i)



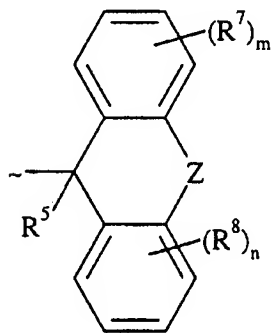
(ii)



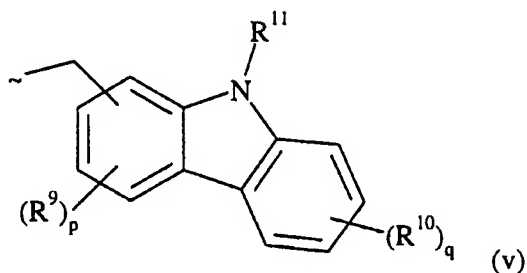
(iii)

R^1 represents a C_{1-6} -alkyl, $C(R^4)_2R^5$, CHR^6R^5 , $Si(R^4)_3$, $C(O)R^6$, or SR^6 group or

10 R^1 represents a group of formula (iv) or (v):



(iv)



(v)

R^2 represents a hydrogen atom or methyl;

15 R^3 represents a hydrogen atom or a C_{1-6} -alkyl group which is optionally substituted by one or more C_{1-6} -alkoxy, C_{1-6} -alkylthio, C_{3-8} -cycloalkyl, and/or phenyl groups (wherein the one or more phenyl groups are optionally substituted by one or more halogen atoms and/or hydroxy, C_{1-4} -alkyl and/or C_{1-4} -alkoxy groups);

R^4 represents phenyl optionally substituted by one or more halogen atoms and/or one or more C_{1-4} -alkoxy, C_{1-4} -alkylthio and/or C_{1-4} -alkyl groups (wherein the one or more alkyl groups are optionally substituted by one or more F atoms);

R^5 represents a hydrogen atom or a C_{1-6} -alkoxy, C_{1-6} -alkylthio, C_{1-6} -alkyl or a phenyl group;

R^6 represents a C_{6-10} -aryl group which is optionally substituted by one or more halogen atoms and/or one or more C_{6-10} -aryl, C_{6-10} -aryloxy, C_{6-10} -arylthio, C_{3-8} -cycloalkyl, C_{1-6} -alkylthio, C_{1-6} -alkyl and/or C_{1-6} -alkoxy groups, each of which substituents are optionally substituted by one or more halogen atoms and/or one or more C_{1-6} -alkyl, phenyl and/or C_{1-6} -alkoxy groups;

R^7 and R^8 each independently represent a halogen atom or a C_{1-4} -alkoxy, C_{1-4} -alkylthio or C_{1-4} -alkyl group (wherein the one or more alkyl groups are optionally substituted by one or more F atoms);

R^9 and R^{10} each independently represent a halogen atom or a C_{1-4} -alkoxy, C_{1-4} -alkylthio, C_{1-4} -alkyl (optionally substituted by a phenyl group) or a C_{3-8} -cycloalkyl group;

R^{11} represents C_{1-6} -alkyl group optionally substituted by phenyl;

Q^1 and Q^2 each independently represent O or S;

Y represents O or a CF_2 , CCl_2 or a CBr_2 moiety;

Z represents a direct bond, O, S, $(CH_2)_t$ (wherein when t is greater than 1, one of the CH_2 moieties is optionally replaced by an O or S atom), $CH_2CH=CH$, $CH_2CH=CHCH_2$ or $CH=CH$;

n, m, p and q each independently represent 0 or an integer from 1 to 4;

t represents an integer from 1 to 4;

• provided that:

(a) when X represents H then Q^1 represents a S atom and R^1 represents a group of formula (iv) where R^5 is hydrogen, and Z is CH_2CH_2 or $CH=CH$;

(b) when R^3 represents H then Y does not represent O;

(c) when X represents a group of formula (i) or (ii) then:

(i) R^1 represents a group of formula (iv) wherein Z represents a direct bond, O, $CH=CH$, or CH_2CH_2 , and R^7 , R^8 , n and m are as defined above; or

(ii) R^1 represents $C(R^4)_2R^5$ wherein R^4 represents phenyl substituted by one or more halogen atoms and/or one or more C_{1-4} -alkoxy, C_{1-4} -alkylthio and/or C_{1-4} -alkyl groups

(wherein the one or more alkyl groups are optionally substituted by one or more F atoms) and R^5 represents a hydrogen atom; or

- (iii) R^1 represents CHR^6R^5 wherein R^6 represents a C_{6-10} -aryl group which is substituted by one or more halogen atoms and/or one or more C_{6-10} -aryl, C_{6-10} -aryloxy, C_{6-10} -arylthio, C_{3-8} -cycloalkyl, C_{1-6} -alkylthio, C_{1-6} -alkyl and/or C_{1-6} -alkoxy groups, each of which optional substituents are optionally substituted by one or more halogen atoms and/or one or more C_{1-6} -alkyl, phenyl and/or C_{1-6} -alkoxy groups and R^5 is as defined above but does not represent phenyl;
- (d) when R^1 represents C_{1-6} -alkyl then Q^1 represents a S atom;
- (e) when R^1 represents CHR^5R^6 then R^5 does not represent phenyl.

- 10 Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

As used herein the term alkyl group, including the alkyl portion of alkoxy and alkylthio groups, includes straight or branched chain alkyl groups. Heterocyclyl or cycloalkyl groups include those comprising of more than one ring having one or two ring atoms in common.

- 20 Aryl groups include fused ring systems for example naphthyl, as well as phenyl groups.

Preferably the compound of the invention forms a pharmaceutically acceptable salt, especially with an alkali metal, an alkaline earth metal and/or $N(R^{12})_4$ wherein each R^{12} represents H or a C_{1-6} -alkyl group, for example n-butyl. Suitable alkali metals include Li, Na or K; suitable alkaline earth metals include Mg or Ca.

Preferably X represents a group of formula (iii) where Y represents a CF_2 , CCl_2 or a CBr_2 moiety, more preferably a CCl_2 moiety and R^3 represents a hydrogen atom.

- 30 Preferably R^1 represents $C(R^4)_2R^5$ or a group of formula (iv).

Preferably R^4 represents phenyl which is substituted by one or more halogen atoms (preferably chlorine) and/or one or more methyl groups; more preferably it is substituted in the 4-position.

Preferably R^5 , R^7 and R^8 each represent hydrogen, methyl, chloro or trifluoromethyl.
More preferably R^5 , R^7 and R^8 each represent hydrogen.

Preferably Q^1 represents a sulphur atom and Q^2 represents an oxygen atom.

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Preferably Z represents a direct bond, O, $(CH_2)_2$ or $CH=CH$, more preferably $CH=CH$.

Particularly preferred compounds according to the invention include:

- monoanhydride of 5-diphenylmethyluridine-5'-phosphate with
10 dichloromethylenebisphosphonic acid;
monoanhydride of 5-(9H-fluoren-9-yl)-4-thiouridine-5'-phosphate with
dichloromethylenebisphosphonic acid;
monoanhydride of 5-(9H-xanthen-9-yl)-4-thiouridine-5'-phosphate with
dichloromethylenebisphosphonic acid;
15 monoanhydride of 5-(5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine-5'-phosphate with
dichloromethylenebisphosphonic acid;
5-(5H-Dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine;
monoanhydride of 5-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine-5'-
phosphate with dichloromethylenebisphosphonic acid;
20 5-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine;
monoanhydride of 5-(1,1-bis(4-methylphenyl)methyl)-4-thiouridine-5'-phosphate with
dichloromethylenebisphosphonic acid;
monoanhydride of 5-(1,1-bis(4-chlorophenyl)methyl)-4-thiouridine-5'-phosphate with
dichloromethylenebisphosphonic acid;
25 monoanhydride of 5-(1,1-bis(3,4-dichlorophenyl)methyl)-4-thiouridine-5'-phosphate with
dichloromethylenebisphosphonic acid;
monoanhydride of 5-(1,1-bis(4-methoxyphenyl)methyl)-4-thiouridine-5'-phosphate with
dichloromethylenebisphosphonic acid;
monoanhydride of 5-(3,6-dimethoxy-9H-fluoren-9-yl)-4-thiouridine-5'-phosphate with
30 dichloromethylenebisphosphonic acid;
monoanhydride of 5-(3-(4-methylphenoxy)phenylmethyl)-4-thiouridine-5'-phosphate with
dichloromethylenebisphosphonic acid;
monohydride of 5-(3-(4-chlorophenoxy)phenylmethyl)-4-thiouridine-5'-phosphate with
dichloromethylenebisphosphonic acid;
35 monoanhydride of 5-(3-(3,4-dichlorophenoxy)phenylmethyl)-4-thiouridine-5'-phosphate
with dichloromethylenebisphosphonic acid;

- monoanhydride of 5-(3-(4-methoxyphenoxy)phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid;
- monoanhydride of 5-((3-methoxy-4-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid;
- 5 monoanhydride of 5-((4-methoxy-3-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid;
- monoanhydride of 5-(4-butoxyphenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid;
- monoanhydride of 5-(9-ethylcarbazol-3-ylmethyl)-4-thiouridine-5'-phosphate with
- 10 dichloromethylenebisphosphonic acid;
- monoanhydride of 5-((4-phenyl)phenylthio)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid;
- monoanhydride of 5-(9-methoxyfluoren-9-yl)uridine-5'-phosphate with dichloromethylenebisphosphonic acid;
- 15 monoanhydride of 5-((4-phenyl)phenylcarbonyl)uridine-5'-phosphate, monoanhydride with dichloromethylenebisphosphonic acid;
- 5-diphenylmethyluridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 5-diphenylmethyluridine-5'-(tetrahydrogen-triphosphate)-P³-mono(n-propyl) ester;
- 5-diphenylmethyluridine-5'-(tetrahydrogen-triphosphate)-P³-mono(2-methoxyethyl) ester;
- 20 5-diphenylmethyluridine-5'-(tetrahydrogen-triphosphate)-P³-monophenylmethyl ester;
- 5-diphenylmethyl-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 5-(1,1-bis(4-methoxyphenyl)methyl)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 5-(1,1-bis(4-methoxyphenyl)methyl)-4-thiouridine-5'-(tetrahydrogen triphosphate)-P³-
- 25 monomethyl ester;
- 5-(1,1-bis(4-methoxyphenyl)methyl)-4-thiouridine-5'-(dihydrogen-phosphate)-monomethyl ester;
- 5-(9H-fluoren-9-yl)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 5-(9H-fluoren-9-yl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 30 5-(9H-fluoren-9-yl)-4-thiouridine 5'-(trihydrogen-diphosphate)-P³-monomethyl ester;
- 5-(9H-fluoren-9-yl)-4-thiouridine-5'-(dihydrogen-phosphate)-monomethyl ester;
- 5-triphenylsilyluridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 5-phenylthiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 5-ethyl-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 35 5-((4-methoxy)phenylthio)uridine-5'-(tetrahydrogen triphosphate)-P³-monomethyl ester;
- 5-((2-phenyl)phenylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;

- 5-((3-phenyl)phenylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
5-((4-phenyl)phenylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
5-(2-naphthylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
5-((3-phenoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-
5 monomethyl ester;
5-((4-phenoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-
monomethyl ester;
5-((3-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-
monomethyl ester;
10 5-((4-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-
monomethyl ester;
5-(4-(1,1-dimethylethyl)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-
monomethyl ester;
5-(4-(1,1-dimethylethyl)phenylmethyl)-4-thiouridine-5'-(dihydrogen-phosphate)-
15 monomethyl ester;
5-((3-methoxy-4-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-
triphosphate)-P³-monomethyl ester; or
5-((3-methoxy-4-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-(trihydrogen-
diphosphate)-P²-monomethyl ester; or a salt thereof.

20

Especially preferred compounds of the invention include:

- monoanhydride of 5-(9H-fluoren-9-yl)-4-thiouridine-5'-phosphate with
dichloromethylenebisphosphonic acid;
monoanhydride of 5-(9H-xanthen-9-yl)-4-thiouridine-5'-phosphate with
25 dichloromethylenebisphosphonic acid;
monoanhydride of 5-(5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine-5'-phosphate with
dichloromethylenebisphosphonic acid;
monoanhydride of 5-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine-5'-
phosphate with dichloromethylenebisphosphonic acid;
30 monoanhydride of 5-(1,1-bis(4-methylphenyl)methyl)-4-thiouridine-5'-phosphate with
dichloromethylenebisphosphonic acid; or
monoanhydride of 5-(1,1-bis(4-chlorophenyl)methyl)-4-thiouridine-5'-phosphate with
dichloromethylenebisphosphonic acid; or salts thereof.

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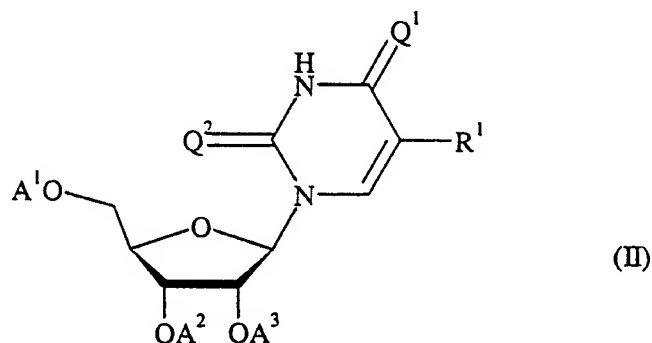
More especially preferred compounds of the invention are:

monoanhydride of 5-(5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid; or
 monoanhydride of 5-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid; or salts thereof.

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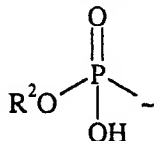
According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I, or a salt thereof, which comprises

- (a) for a compound of formula (I) wherein X represents H, deprotecting a compound of formula

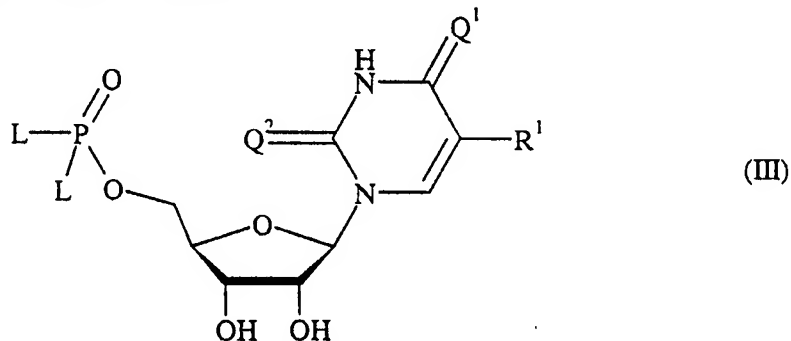


wherein R^1 , Q^1 and Q^2 are as defined above and A^1 , A^2 and A^3 each independently represent a protecting group;

- 15 (b) for a compound of formula (I) wherein X represents

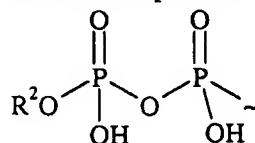


wherein R^2 is as defined above, reacting the product of step (a) with a phosphorylating agent $P(O)L_3$ wherein each L is the same or different and represents a leaving group, to yield an intermediate of formula



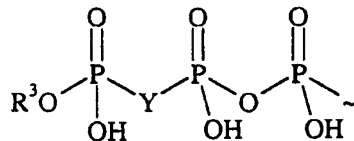
wherein L, Q¹, Q² and R¹ are as defined above, and either hydrolysing the intermediate of formula (III) thus obtained under alkaline conditions or reacting it with MeOH followed by alkaline hydrolysis;

- 5 (c) for a compound of formula (I) wherein X represents

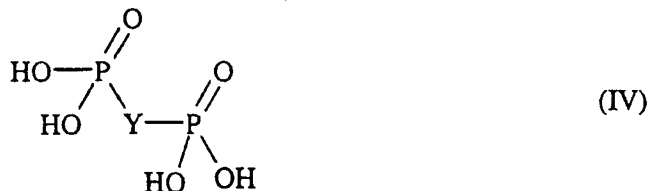


- wherein R² is as defined above, hydrolysing an intermediate of formula (III) as defined above and then reacting it with a phosphorylating agent P(O)L₃ as defined above, and either hydrolysing the product under alkaline conditions or reacting it with MeOH followed by alkaline hydrolysis;
- 10

- (d) for a compound of formula (I) wherein X represents

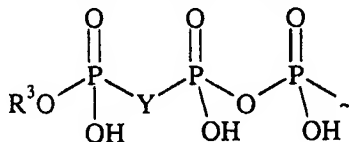


- wherein R³ represents H and Y is as defined above, reacting an intermediate of formula (III) as defined above with a salt of a compound of formula
- 15



wherein Y is as defined above followed by alkaline hydrolysis; or

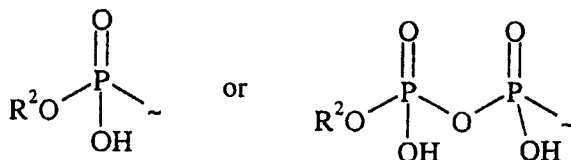
- (e) for a compound of formula (I) wherein X represents



- wherein R³ is as defined for the compound of formula (I) but does not represent H and Y is as defined above, reacting the product of step (d) with a phosphorylating agent P(O)L₃ as defined above, and reacting the product with R³OH wherein R³ is as defined above; and, optionally
- 20
- 25

(f) forming a salt.

A compound of formula (I) wherein X represents:



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wherein R^2 is as defined above may also be obtained as by-products from step (e).

The invention further provides an intermediate of formula (II) wherein its substituents are as defined above, provided that R^1 does not represent C_{1-6} -alkyl, $\text{C}(\text{O})\text{R}^6$, CHR^5R^6 or SR^6 wherein R^6 represents unsubstituted phenyl and R^5 does not represent a H atom. A^1 , A^2 and A^3 preferably represent $(\text{C}_{1-6}\text{-alkyl})_3\text{Si}$ (especially t-butyldimethylsilyl), wherein the silyl groups represented by A^1 and A^2 are optionally connected via an O atom so as to complete a ring.

15 The deprotection reaction in step (a) of the process of the invention may be carried out using methods generally known in the art (see "Protective Groups in Organic Chemistry" by Theodora Greene, John Wiley and Sons Inc., 1981). Step (a) is preferably carried out using, for example, a fluoride ion source, for example tetra-n-butylammonium fluoride or a hydrogen fluoride/pyridine complex, or caesium fluoride, in a suitable aprotic solvent, such as tetrahydrofuran, acetonitrile, diethylether or dichloromethane.

In steps (b) and (c), the phosphorylating agent is preferably one where L represents halogen, more preferably chlorine. In step (e), the phosphorylating agent is preferably one where L represents halogen (more preferably chlorine) or O-phenyl; most preferably the agent is $\text{P}(\text{O})(\text{OPh})_2\text{Cl}$.

The reaction in steps (b) and (c) with a phosphorylating agent is preferably carried out in the presence of a base, such as 1,8-bis(dimethylamino)naphthalene, and/or an inert base such as a tri- C_{1-8} -alkylamine, for example triethylamine, tri-n-butylamine, N,N-diethylisopropylamine or tri-n-octylamine. The reaction is preferably carried out in a solvent, preferably a dipolar aprotic solvent, for example, trimethylphosphate, triethylphosphate, acetonitrile, and preferably at a temperature of from -20 to 20°C , more preferably from -5°C to 5°C .

30

In steps (b), (c) and (d), the compound of formula (III) is preferably not isolated but is reacted *in situ*. Similarly in step (e) the product of step (d) is preferably not isolated but reacted *in situ*.

5

In step (d) where Y in the compound of formula (IV) does not represent O, the reaction time is preferably from 2 to 8 hours and the reaction temperature is preferably from 0 to 40°C, more preferably from 0 to 25°C. The alkaline hydrolysis step is preferably carried out for 5 to 48 hours.

10

In step (d) where Y in the compound of formula (IV) represents O, the reaction time is preferably from 2 to 10 minutes (more preferably about 5 minutes) and the reaction temperature is preferably from -5 to 5°C, more preferably about 0°C.

15

In step (e) the phosphorylation reaction time is preferably from 1 to 5 hours (more preferably about 2.5 hours) in a suitable aprotic solvent (preferably 1,4-dioxane) preferably at a temperature of from 10 to 40°C (more preferably about 25°C). The resulting intermediate is reacted with R³OH in a suitable solvent (preferably pyridine) for preferably from 1 to 5 hours (more preferably about 2.5 hours).

20

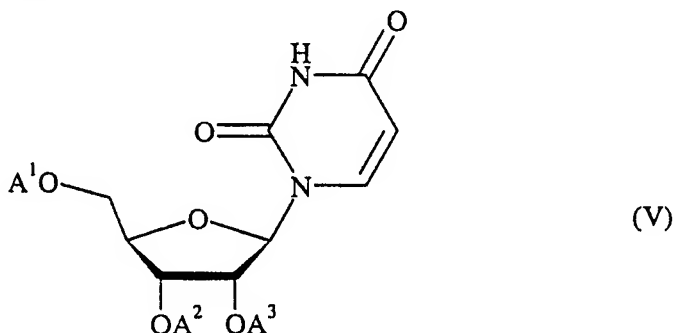
The salt of the compound of formula (IV) as defined above used in step (d) is preferably the mono tri-n-butylammonium salt.

In steps (b), (c) and (d), hydrolysis is preferably a base-catalysed hydrolysis; for example using aqueous triethyl ammonium bicarbonate, Na₂CO₃, NaHCO₃, K₂CO₃, KHCO₃, or any alkaline earth metal carbonate salt.

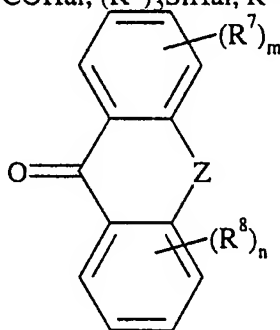
Salts of the compounds of formula (I) may be formed by reacting the free acid, or a salt thereof, with one or more equivalents of the appropriate base (for example ammonium hydroxide optionally substituted by C₁₋₆-alkyl or an alkali metal or alkaline earth metal hydroxide). The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. water, alcohol or acetone, which may be removed *in vacuo*, or by freeze drying. The reaction may also be a metathetical process or it may preferably be carried out on an ion exchange resin. The non-toxic physiologically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

A compound of formula (II) wherein Q^1 and/or Q^2 represent S may be synthesised from a compound of formula (II) wherein Q^1 and Q^2 represent O using standard thiation conditions for conversion of uridine and thymidine nucleosides into their corresponding thio-nucleoside derivatives (see "Chemistry of Nucleosides and Nucleotides" edited by Leroy B. Townsend, Plenum Press volume 1). For example conditions such as phosphorus pentasulphide or Lawesson's reagent in inert solvent(s) such as pyridine, toluene, xylene, tetrahydrofuran, and/or 1,4-dioxane at temperatures of from 50 °C to 130 °C could be used.

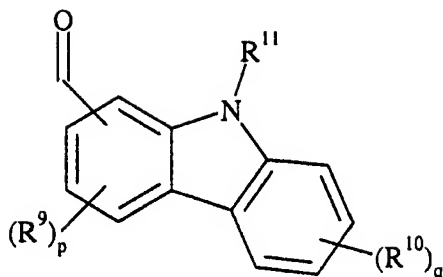
Compounds of formula (II) may be synthesised directly (using the procedure described in Tetrahedron Letters, 1987, 28 (1), 87-90 or a modified procedure thereof) by metallation of the protected uridine of formula



- wherein A^1 , A^2 and A^3 are as defined above, using for example alkylmetallic reagents such as n-butyllithium, sec-butyllithium, tert-butyllithium or metallic dialkylamides such as lithium diisopropylamide, lithium-, sodium- or potassium-hexamethyldisilazane, in the absence or presence (preferably presence) of metal chelating agents such as N,N,N',N'-tetramethylethylenediamine, hexamethyl-phosphoramide. Preferably sec-butyl lithium with N,N,N',N'-tetramethylethylenediamine are used. Metallation is followed by reacting the intermediate organometallic species with an electrophile such as $(C_{1-5}\text{-alkyl})\text{-CHO}$, $R^4C(O)R^4$, R^6CHO , R^6SSR^6 , R^6COHal , $(R^4)_3SiHal$, R^6CH_2Hal , $(C_{1-6}\text{-alkyl})\text{-Hal}$ or



or



wherein Z, R⁴, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, n, m, p and q are as defined above and Hal represents a halogen atom, preferably bromine or iodine. The metallation is generally carried out at low temperatures, for example from -40 °C to -78 °C, and in dried solvents, for example tetrahydrofuran, diethylether, glyme and/or diglyme, under an inert atmosphere, for example under nitrogen or argon gas.

Where the electrophile was an aldehyde or a ketone and R⁵ represents a hydrogen atom, the metallation is followed by reduction using standard reducing conditions suitable to remove a hydroxyl group. For example the reducing agents may be hydrogen gas in the presence of a catalyst, such as platinum, platinum oxide, palladium, palladium oxide, Raney Nickel or rhodium, on a support, such as charcoal, using an alcohol, such as ethanol, or an ester, such as ethyl acetate, as the reaction solvent, or a mixture of solvents, at normal or elevated pressure. The preferred temperature is room temperature. The preferred pressure is from 1 to 3 atmospheres. The preferred reducing agent is triethylsilane, in the presence of a strong acid, such as trifluoroacetic acid, or a Lewis acid, such as a boron trifluoride ethyl etherate complex in a suitable inert solvent, such as dichloromethane, chloroform, 1,2-dichloroethane. Alternatively the reduction may be performed by electrons generated *in situ* by dissolving a suitable metal, for example iron, zinc, tin or magnesium, in a suitable acid, for example acetic acid, formic acid, dilute hydrochloric acid, dilute sulphuric acid, for example at a temperature of from 20 to 120 °C.

Where the electrophile was an aldehyde or a ketone and R⁵ does not represent a hydrogen atom, the metallation is followed by:

- (i) where R⁵ represents C₁₋₆-alkoxy reaction with a C₁₋₆-alkyl alcohol using the method of S Kim, K N Chung and S Yang JOC, 1987, 52, 3917-3919;
- (ii) where R⁵ represents C₁₋₆-alkylthio, reaction with a C₁₋₆-alkyl thioalcohol in the presence of ZnI₂ (Y Guindon, R Frenette, R Fortin, J Rokach, JOC, 1983, 48, 1357-1359);

(iii) where R^5 represents C_{1-6} -alkyl or a phenyl group, reaction with a suitable chlorinating agent such as trimethylsilyl chloride (Nucleosides and Nucleotides, 1993, vol 12, issues 3 & 4, pp 305-321) or thionyl chloride with pyridine, followed by reaction with the
5 appropriate trialkyl or triphenyl thallide (I E Markó, M L Kantam, T Lett, 1991, 32, 2255-2258).

Compounds of formula (II) wherein R^1 represents SR^6 wherein R^6 is as defined above, can also be synthesised directly from 5-mercuriuridine using a compound of formula R^4SSR^4
10 and palladium tetrachloride using the method described in Journal of Organic Chemistry 1991, 56, (19), 5598 or a modified procedure thereof.

The compounds of the invention have been submitted to the assay outlined in Example A and have been found to be P2 7-TM G-protein receptor antagonists, particularly to the
15 P2Y2 receptor. Accordingly they are useful in therapy and are, in particular, indicated for use as anti-inflammatory agents useful in a number of inflammatory diseases such as asthma, inflammatory bowel disease, ARDS, psoriasis, rheumatoid arthritis, myocardial ischaemia, COPD, cystic fibrosis, arteriosclerosis, restenosis, periodontal disease, septic shock, osteoarthritis and stroke. ATP receptors have also been reported on tumour cells and
20 may be involved in the development of cancer. Antagonists may therefore be useful in treatment of cancer.

The invention provides in a further aspect a method of treating an inflammatory condition which comprises administering to a patient in need of therapy, a therapeutically effective
25 amount of a compound of the invention. The compounds of the invention can be co-administered with other anti-inflammatory agents.

According to the invention there is further provided use of the compounds of the invention in the manufacture of a medicament for use in the treatment of an inflammatory condition.
30

The compounds may be administered orally, topically e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols and dry powder formulations, e.g. Turbuhaler® formulations or by parenteral administration in the form of sterile parenteral solutions or suspensions.
35

The invention further provides a pharmaceutical composition comprising a compound according to the present invention in association with a pharmaceutically acceptable excipient and/or adjuvant. . Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction. For example a chelating or
5 sequestering agent, an antioxidant, a tonicity adjusting agent, a pH modifying agent and/or a buffering agent are suitable additives.

The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated
10 dry powder inhaler.

A pharmaceutical composition according to the present invention could optionally be prepared in freeze dried form using any lyophilisation techniques commonly used within the pharmaceutical area. Upon use but before administration, such pharmaceutical
15 compositions are generally reconstituted in a pharmaceutically acceptable excipient. Preferably a solution of the pharmaceutical composition according to the invention obtained after reconstitution is an isotonic solution. Such a pharmaceutical composition according to the present invention when reconstituted is preferably administered by injection, for example intravenously, subcutaneously or intramuscularly.

20 The invention is illustrated by the following examples which should not be interpreted as limiting the invention. In the examples the NMR spectra were measured on a Varian Unity Inova 300 spectrometer and the MS spectra were measured as follows: EI spectra were obtained on a VG 70-250S or Finnigan Mat Incos-XL spectrometer, FAB spectra were
25 obtained on a VG70-250SEQ spectrometer, ESI and APCI spectra were obtained on Finnigan Mat SSQ7000 or a Micromass Platform spectrometer. Preparative HPLC separations were generally performed using a Novapak[®], Bondapak[®] or Hypersil[®] column packed with BDSC-18 reverse phase silica; chromatography was generally performed using Matrex Silica 60[®] (35-70 micron) or Prolabo Silica gel 60[®] (35-75 micron) suitable
30 for flash silica gel chromatography.

Example 1**Trisodium salt of the monoanhydride of 5-diphenylmethyluridine-5'-phosphate with dichloromethylenebisphosphonic acid.**

5

(i) To a solution of 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine (12g) in dry tetrahydrofuran (300ml) at -78°C under a nitrogen atmosphere was added N,N,N',N'-tetramethylenediamine (6.8ml) followed by sec-butyllithium (35ml) (1.3M in cyclohexane) dropwise over 10 minutes. After 1 hour the reaction was quenched with a solution of benzophenone (7.5g) dissolved in dry tetrahydrofuran (40ml). After a further 1 hour the cooling bath was removed and the mixture was allowed to warm to approximately -10°C before quenching with water (50ml). The reaction mixture was extracted with dichloromethane (200ml) three times and the organic extracts were pooled, dried over magnesium sulphate and evaporated to dryness to leave a pale yellow oil. The product was purified by silica-gel chromatography eluting with iso-hexane and ethyl acetate mixtures to give 5-(hydroxy-(1,1-diphenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine as a colourless foam (9.0g).
MS: FAB: (+Rb): m/e 853/5 (M+Rb)⁺

(ii) The product of step (i) (8.9g) was dissolved in dichloromethane (100ml) and triethylsilane (2ml). Trifluoroacetic acid (8.9ml) was added dropwise over 5 minutes and the mixture was stirred for a further 20 minutes. The volatiles were removed under reduced pressure and any residual traces were removed by addition of toluene (50ml) and evaporation under reduced pressure (three times). The residual gum was treated with tetra-n-butylammonium fluoride (35ml of a 1M solution in tetrahydrofuran) for 1 hour at room temperature. The volatiles were removed under reduced pressure and the gummy residue purified by silica-gel chromatography eluting with chloroform-methanol mixtures to give 5-diphenylmethyluridine as a white solid (4g).
MS: FAB(+ve): m/e 411 (M+1)⁺

30

(iii) The product of step (ii) (0.44g) and 1,8-bis(dimethylamino)naphthalene (0.37g) were dissolved in dry triethylphosphate (5ml) and then cooled to 0°C under a nitrogen atmosphere. Phosphorous oxychloride (0.16ml) was added dropwise and the resulting mixture stirred at 0° C for 3 hours before addition of a pre-formed solution of the mono tri-n-butylammonium salt of dichloromethylenebisphosphonic acid (1.16g) (Blackburn *et al*, J Chem Soc Chem Commun, 1981, 22, 1188-1190) with tri-n-butylamine (0.64ml) in

35

triethylphosphate (8ml). After 5 minutes the mixture was allowed to reach room temperature by removing the cooling bath. After 4 hours the mixture was quenched by addition of aqueous sodium bicarbonate (2.5g) solution (50 ml) and then stirred for a further 24 hours. The mixture was extracted twice with diethyl ether (50ml). The aqueous phase was concentrated under reduced pressure and the residue purified by ion-exchange chromatography (DEAE Sephadex eluting with 0 - 0.5M triethylammonium bicarbonate solution). Fractions containing product were pooled, lyophilised and the residue was dissolved in water and passed down an ion-exchange column (Dowex-50 Na⁺ form). The UV (254 nm) active fractions were pooled and lyophilised and the residue was purified by reverse phase chromatography (C18 Sep-pak silica) eluting with water. Fractions containing the product were pooled and lyophilised to leave the trisodium salt of the monoanhydride of 5-diphenylmethyluridine-5'-phosphate with dichloromethylenebisphosphonic acid as a white powder (0.137g).
³¹P NMR δ (D₂O): 8.94(d), 0.65(dd), -9.55(d);
MS: FAB (+ve): m/e 783 (M+1)⁺

Example 2

Triammonium salt of the monoanhydride of 5-(9H-fluoren-9-yl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

(i) 5-(9-Hydroxyfluoren-9-yl)-2',3',5'-tris-O-(1,1-dimethylethyl)dimethylsilyluridine was prepared from 2',3',5'-tris-O-(1,1-dimethylethyl)dimethylsilyluridine according to the method of Example 1 step (i) (using 9-fluorenone instead of benzophenone) as a colourless foam.
MS: FAB(+Rb): m/e: 854/852 (M+Rb)

(ii) The product of step (i) (10.26g) was dissolved in dichloromethane (200ml) and triethylsilane (2.34ml) and cooled to 0°C before treating with boron trifluoride diethyl-etherate (3.3ml) dropwise. After 30 minutes, the reaction was quenched with aqueous sodium bicarbonate (12g in 300ml of water). The organic phase was collected and dried over magnesium sulphate and the solvent was evaporated under reduced pressure. The residue was dissolved in dry dimethylformamide (40ml) and treated with imidazole (1.82g) and t-butyltrimethylsilylchloride (2.02g). After stirring for 16 hours, the mixture was quenched with water (100ml) and the product was extracted into iso-hexane. The solvent was removed under reduced pressure and the residue which was 5-(9H-fluoren-9-yl)-

2',3',5'-tris-O-(1,1-dimethylethyl)dimethylsilyl)uridine (8.05g) was used directly in the next step.

(iii) The product of step (ii) (8.05g) was dissolved in dry pyridine (200ml) under a nitrogen atmosphere and treated with phosphorus pentasulphide (11.89g) before refluxing for 16 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue was quenched with saturated aqueous sodium bicarbonate solution followed by extraction of the product into ethyl acetate (three times). The combined extracts were dried over magnesium sulphate and the solvent was removed under reduced pressure. The remaining residue was purified by silica-gel chromatography eluting with iso-hexane/ethyl acetate mixtures to give 5-(9H-fluoren-9-yl)-2',3',5'-tris-O-(1,1-dimethylethyl)dimethylsilyl)-4-thiouridine as a yellow foam (5.50 g).

MS: FAB(-ve): 765(M-1).

(iv) The product of step (iii) (5.5g) was treated with tetra-n-butyl ammonium fluoride (6.19g) in tetrahydrofuran (24ml) and the mixture stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica-gel eluting with 10% methanol in ethyl acetate to give 5-(9H-fluoren-9-yl)-4-thiouridine as a pale yellow solid (3.43g).

MS: EI: 424(M⁺)

(v) The triammonium salt of the monoanhydride of 5-(9H-fluoren-9-yl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iii) (with further purification by reverse phase HPLC using 10% methanol in 0.5% aqueous ammonium acetate) as a yellow powder.

³¹P NMR δ (D₂O): 8.68(d), 0.18(dd), -9.9(d);

MS: FAB (-ve): m/e 729/731/733 (M-1)

Example 3

Tetrasodium salt of the monoanhydride of 5-(9H-xanthen-9-yl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

(i) 5-(9-Hydroxyxanthen-9-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to

the method of Example 1 step (i) (using xanthone instead of benzophenone) as a pale yellow solid.

MS: FAB(-ve): 781(M-1)

- 5 (ii) 5-(9H-Xanthen-9-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 2 step (ii) as a pale yellow foam.

MS: FAB(-ve): 765(M-1)

- 10 (iii) 5-(9H-Xanthen-9-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow solid.

MS: FAB(-ve): 781(M-1).

- 15 (iv) 5-(9H-Xanthen-9-yl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 2 step (iv) as a light-sensitive yellow solid.

MS: FAB(+ve): 441(M+1).

- 20 (v) The tetrasodium salt of the monoanhydride of 5-(9H-xanthen-9-yl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iii) as a yellow powder.

^{31}P NMR δ (D_2O): 9.44(d), 3.45(dd), -9.78(d);

MS: FAB (+ve): m/e 835/837/839 (M+1)

25 **Example 4**

The tetrasodium salt of the monoanhydride of 5-(5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

- 30 (i) 5-(5-Hydroxy-(dibenzo[a,d]cyclohepten)-5-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine according to the method of Example 1 step (i) (using dibenzosuberone instead of benzophenone) as a white foam.

MS: FAB(-ve): 791(M-1)

(ii) 5-(5H-Dibenzo[a,d]cyclohepten-5-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 2 step (ii) as a colourless foam.

MS: FAB(-ve): 775(M-1)

(iii) 5-(5H-Dibenzo[a,d]cyclohepten-5-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam.

MS: FAB(-ve): 791(M-1)

(iv) The product of step (iii) (0.75g) was dissolved in acetonitrile (10ml) and treated with a 1:1 hydrofluoric acid-pyridine complex (6ml). After 3 hours, the mixture was quenched with saturated aqueous sodium carbonate solution (100ml) and the product was extracted into ethyl acetate. The organic phase was collected, dried over magnesium sulphate and the solvent was removed under reduced pressure. The residue was purified by flash silica-gel chromatography to afford 5-(5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine as a yellow powder (0.36g).

MS: FAB(+ve): 451(M+1)

(v) The tetrasodium salt of the monoanhydride of 5-(5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine-5'-phosphate with dichloromethylenbisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iii) as a yellow powder.

^{31}P NMR δ (D_2O): 9.13(d), 3.88(dd), -10.05(d);

MS: FAB (+ve): m/e 845/847/849 (M+1)

Example 5

5-(5H-Dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine

Prepared as described in Example 4 step (iv).

^1H NMR δ (d_6 -DMSO): 12.63(bs, 1H), 7.63(d, 1H), 7.58(d, 1H), 7.42-7.27(m, 6H), 7.02(m, 3H), 5.87(s, 1H), 5.71(d, 1H), 5.43(d, 1H), 5.18(d, 1H), 4.82(t, 1H), 3.76(m, 3H), 3.36(m, 1H), 3.27(m, 1H)

MS: FAB(+ve): 451(M+1)

Example 6

Tetrasodium salt of the monoanhydride of 5-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

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(i) 5-((10,11-Dihydro-5-hydroxy-5H-dibenzo[a,d]cyclohepten)-5-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using dibenzosuberone instead of benzophenone) as a pale yellow oil.

10 MS: FAB(-ve): 793(M-1)

(ii) 5-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 2 step (ii) as a pale yellow foam.

15 MS: FAB(-ve): 777(M-1).

(iii) 5-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam.

20 MS: FAB(-ve): 793(M-1).

(iv) 5-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 4 step (iv) as a yellow solid.
MS: APCI +loop: 453(M+1)

25

(v) The tetrasodium salt of the monoanhydride of 5-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iv) as a yellow solid.

30 ³¹P NMR δ (D₂O): 9.93(d), 3.67(dd), -9.38(d);

MS: FAB (+ve): 847/849/851 (M+1)

Example 7**5-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine**

Prepared as described in Example 6 step (iv).

- 5 ^1H NMR δ (d_6 -DMSO): 12.72(bs, 1H), 7.41(d, 1H), 7.35(d, 1H), 7.13(m, 7H), 5.78(d, 1H), 5.6(s, 1H), 5.45(d, 1H), 5.15(d, 1H), 4.68(t, 1H), 3.79(q, 1H), 3.69(q, 1H), 3.64(m, 1H), 3.41(m, 2H), 3.18(m, 2H), 2.78(m, 2H), 2.78(m, 2H)

MS: APCI +loop: 453(M+1)

10 **Example 8**

Tetrasodium salt of the monoanhydride of 5-(1,1-bis(4-methylphenyl)methyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

- 15 (i) 5-(Hydroxy-1,1-bis(4-methylphenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine according to the method of Example 1 step (i) (using 4,4'-dimethylbenzophenone instead of benzophenone) as a colourless foam.

MS: FAB(-ve): 795(M-1)

- 20 (ii) The product of step (i) (10.84g) was dissolved in dichloromethane (100ml), triethylsilane (2.6ml) and treated with trifluoroacetic acid (2.1ml). After stirring for 1 hour, the solvent was removed under reduced pressure and any remaining traces removed by azeotroping with toluene (two times). The residue was dissolved in dry dimethylformamide (80ml) and treated with imidazole (1.77g) and t-butyldimethylsilylchloride (2.11g). After
25 stirring for 16 hours, the mixture was quenched with water and the product extracted into ethyl acetate. The organic phase was collected and the solvent removed under reduced pressure. The residue was purified by flash silica-gel chromatography to afford 5-(1,1-bis(4-methylphenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine as a colourless foam (8.59g).

- 30 MS: FAB(-ve): 779(M-1)

(iii) 5-(1,1-Bis(4-methylphenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam.

- 35 MS: FAB(-ve): 795(M-1)

(iv) 5-(1,1-Bis(4-methylphenyl)methyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 4 step (iv) as a yellow solid.

MS: FAB(+ve): 455(M+1)

- 5 (v) The tetrasodium salt of the anhydride of 5-(1,1-bis(4-methylphenyl)methyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iv) as a yellow powder.

^{31}P NMR δ (D_2O): 9.92(d), 3.71(dd), -9.35(d);

MS: FAB (+ve): 849/851/853 (M+1)

10

Example 9

Tetrasodium salt of the monoanhydride of 5-(1,1-bis(4-chlorophenyl)methyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

- 15 (i) 5-(1,1-Bis(4-chlorophenyl)hydroxymethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine according to the method of Example 1 step (i) (using 4,4'-dichlorobenzophenone instead of benzophenone) to afford the product as a colourless foam.

20 MS: FAB(-ve): 836/838/840(M-1)

- (ii) 5-(1,1-Bis(4-chlorophenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 8 step (ii) as a colourless foam.

25 MS: FAB(-ve): 820/822/824(M-1).

- (iii) 5-(1,1-Bis(4-chlorophenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam.

30 MS: FAB(-ve): 836/838/840(M-1).

- (iv) 5-(1,1-Bis(4-chlorophenyl)methyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 4 step (iv) as a yellow solid.

MS: FAB(+ve): 495/497/499(M+1)

35

(v) The tetrasodium salt of the monoanhydride of 5-(1,1-bis(4-chlorophenyl)methyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iv) as a yellow powder.

^{31}P NMR δ (D_2O): 9.40(d), 1.87(dd), -9.38(d);

5 MS: ESI-loop m/e: 399/400/401/402(M-2)

Example 10

The tetrasodium salt of the monoanhydride of 5-(1,1-bis(3,4-dichlorophenyl)methyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

10

(i) To a solution of 3,4-dichloriodobenzene (20g) in dry tetrahydrofuran (300ml) under a nitrogen atmosphere at -78°C was added 1.7M t-butyllithium in pentane (86ml), dropwise over 10 minutes. After 30 minutes, the yellow solution was briefly allowed to reach -30°C by removing the cooling bath. The mixture was returned to -78°C before adding quickly a
15 solution of 3,4-dichlorobenzonitrile (13g) in dry tetrahydrofuran (50ml). The cooling bath was removed and the mixture allowed to reach room temperature. After 1 hour, the mixture was quenched with saturated aqueous ammonium chloride solution (300ml). The mixture was stirred at room temperature for a further 16 hours and the product extracted
20 into ethyl acetate. The solvent was removed under reduced pressure. The residue was purified by silica-gel chromatography eluting with diethyl ether/iso-hexane mixtures to afford 3,4,3',4'-tetrachlorobenzophenone as a beige solid. This was triturated with iso-hexane and filtered to afford a pure sample.

MS: EI: 318/320/322/324/326 (M^+)

25

(ii) 5-(1,1-Bis(3,4-dichlorophenyl)hydroxymethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris((1,1-dimethylethyl)-dimethylsilyl)uridine according to the method of Example 1 step (i) (using the product of step (i) instead of benzophenone) as a pale yellow foam.

MS: APCI+loop: 887/889/891($\text{M}+\text{H}-\text{H}_2\text{O}$)

30

(iii) 5-(1,1-Bis(3,4-dichlorophenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine was prepared from the product of step (ii) according to the method of Example 2 step (ii) as a colourless foam.

MS: APCI+loop: 889/891/893(M+1)

35

(iv) 5-(1,1-Bis(3,4-dichlorophenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 2 step (iii) as a yellow foam.

MS: FAB(-ve): 903/905/907/909(M-1)

5

(v) 5-(1,1-Bis(3,4-dichlorophenyl)methyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 4 step (iv) as a yellow solid.

MS: FAB(-ve): 563/564/565/566(M-1)

10 (vi) The tetrasodium salt of the monoanhydride of 5-(1,1-bis(3,4-dichlorophenyl)methyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (v) according to the method of Example 1 step (iii) as a yellow powder.

³¹P NMR δ (D₂O): 9.56(d), 2.65(dd), -9.18(d);

MS: ESI-loop: 867/869/871/873/875(M-1)

15

Example 11

Tetrasodium salt of the monoanhydride of 5-(1,1-bis(4-methoxyphenyl)methyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

20 (i) 5-(Hydroxy-1,1-bis(4-methoxyphenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine according to the method of Example 1 step (i) (using 4,4'-dimethoxybenzophenone instead of benzophenone) as a colourless foam.

MS: FAB: 811(M+H-H₂O)

25

(ii) 5-(1,1-Bis(4-methoxyphenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 2 step (ii) as colourless foam.

MS: FAB(+ve): 813(M+1), FAB(-ve): 811(M-1)

30

(iii) 5-(1,1-Bis(4-methoxyphenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam.

MS: FAB(-ve): 827(M-1)

35

(iv) 5-(1,1-Bis(4-methoxyphenyl)methyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 2 step (iv) as a yellow solid.

MS: APCI(+ve): 487(M+1)

- 5 (v) The tetrasodium salt of the monoanhydride of 5-(1,1-bis(4-methoxyphenyl)methyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iii) as a yellow powder.

³¹P NMR δ (D₂O): 8.98(d), 1.26(dd), -9.5(d);

MS: FAB(+ve): 859/861/863(M+1)

10

Example 12

Tetrasodium salt of the monoanhydride of 5-(3,6-dimethoxy-9H-fluoren-9-yl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

- 15 (i) 5-(3,6-Dimethoxy-9-hydroxyfluoren-9-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine according to the method of Example 1 step (i) (using 3,6-dimethoxyfluoren-9-one (J. Org. Chem. (1993) 58 (16), 4398-4404) instead of benzophenone) as a pale yellow solid.

20 ¹H NMR: δ (CDCl₃): 8.40(s, 1H), 7.32(d, 2H), 7.06(d, 2H), 6.72(dd, 2H), 5.75(d, 1H), 4.05(m, 1H), 3.9(m, 1H), 3.83(m, 1H), 3.80(s, 6H), 3.45(m, 2H), 0.6(m, 27H), 0.0(m, 18H)

- (ii) 5-(3,6-Dimethoxy-9H-fluoren-9-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 2 step (ii) as a pale yellow powder.

25 MS: FAB(-ve): 696(M-1)

- (iii) 5-(3,6-Dimethoxy-9H-fluoren-9-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam and was used directly in the next step.

30

(iv) 5-(3,6-Dimethoxy-9H-fluoren-9-yl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 2 step (iv) as a yellow solid.

MS: FAB(+ve): 485(M+1)

35

(v) The tetrasodium salt of the monoanhydride of 5-(3,6-dimethoxy-9H-fluoren-9-yl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iii) as a yellow powder.

^{31}P NMR δ (D_2O): 9.71(d), 3.58(dd), -9.5(d);

5 MS: ESI-loop: 793/791/789(M-1)

Example 13

Tetrasodium salt of the monoanhydride of 5-(3-(4-methylphenoxy)phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

10

(i) 5-(Hydroxy-(3-((4-methylphenoxy)phenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using 3-(4-methylphenoxy)-benzaldehyde instead of benzophenone) as a colourless foam.

15 MS: FAB(-ve): 797(M-1).

(ii) 5-(3-(4-Methylphenoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 2 step (ii) as a colourless oil.

20 MS: FAB(-ve): 781(M-1)

(iii) 5-(3-(4-Methylphenoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam.

25 MS: APCL+loop: 799(M+1)

(iv) 5-(3-(4-Methylphenoxy)phenylmethyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 2 step (iv) as a yellow foam.

MS: FAB: (+ve): 457(M+1)

30

(v) The tetrasodium salt of the monoanhydride of 5-(3-(4-methylphenoxy)phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (iii) according to the method of Example 1 step (iii) as a yellow powder.

^{31}P NMR δ (D_2O): 9.44(d), 3.45(dd), -9.78(d);

35 MS: FAB(+ve): 835/837/839(M+1)

Example 14

Tetrasodium salt of the monohydride of 5-(3-(4-chlorophenoxy)phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

- 5 (i) 5-((3-(4-Chlorophenoxy)phenyl)hydroxymethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using 3-(4-chlorophenoxy)-benzaldehyde instead of benzophenone) as a pale yellow oil.
¹H NMR δ (CDCl₃): 8.39(s, 1H), 7.42(s, 1H), 7.19-7.26(m, 5H), 7.00(m, 1H), 6.79-6.85(m, 4H), 5.89-5.91(d, 1H), 5.48-5.49(d, 1H), 3.93-3.95(m, 2H), 3.55-3.67(m, 2H), 3.36-3.43(dd, 1H), 0.77-0.87(m, 27H), -0.14-0.07(m, 18H).
- 10 (ii) 5-(3-(4-Chlorophenoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine was prepared from the product of step (i) according to the method of
15 Example 2 step (ii) as a pale yellow foam and used directly in the next step.
- (iii) 5-(3-(4-Chlorophenoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam.
20 ¹H NMR δ (CDCl₃): 9.32(s, 1H), 7.38(s, 1H), 7.22-7.15(m, 3H), 6.91-6.74(m, 5H), 5.88-5.86(d, 1H), 4.08-4.02(m, 1H), 3.97-3.93(m, 2H), 3.87-3.83(d, 1H), 3.80-3.76(d, 1H), 3.72-3.68(dd, 1H), 3.61-3.57(dd, 1H), 0.90-0.74(m, 27H), -0.12-0.6(m, 18H)
- (iv) 5-(3-(4-Chlorophenoxy)phenylmethyl)-4-thiouridine was prepared from the product of
25 step (iii) according to the method of Example 2 step (iv) as a yellow solid.
MS: APCI-loop: 475/477(M-1)
- (v) The tetrasodium salt of the monoanhydride of 5-(3-(4-chlorophenoxy)phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from
30 the product of step (iv) according to the method of Example 1 step (iii) as a yellow powder.
³¹P NMR δ (D₂O): 9.9(d), 3.7(dd), -9.45(d)
MS: ESI-loop: 390/391/392(M²⁺)

Example 15

Tetrasodium salt of the monoanhydride of 5-(3-(3,4-dichlorophenoxy)phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

- 5 (i) 5-((3-(3,4-Dichlorophenoxy)phenyl)hydroxymethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using 3-(3,4-dichlorophenoxy)benzaldehyde instead of benzophenone) as a colourless foam.
- ¹H NMR δ (CDCl₃): 8.3 (m, 0.5H), 7.6 (2xs, 0.5H), 7.4-6.8 (m, 7H), 6.0 (t, 0.5H), 5.6 (m, 0.5H), 4.7 (s, 0.5H), 4.1 (m, 2H), 4.0 (d, 1H), 3.7 (m, 1H), 3.5 (m, 0.5H), 0.9 (m, 27H), 0.0 (m, 18H) mixture of diastereoisomers 60/40
- 10 (ii) 5-(3-(3,4-Dichlorophenoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 2 step (ii) as a colourless foam and was used directly in the next step.
- 15 (iii) 5-(3-(3,4-Dichlorophenoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam.
- 20 ¹H NMR δ (CDCl₃): 9.3(s,1H), 7.43(bs,1H), 7.25-7.3(m, 1H), 7.15-7.25(m, 1H), 7.0-6.9(m, 2H), 6.9-6.7 (m, 3H), 5.9(bs, 1H), 4.15-3.5(m, 7H), 0.83(s, 9H), 0.78(s, 9H), -0.2-0.5(m, 18H).
- (iv) 5-(3-(3,4-Dichlorophenoxy)phenylmethyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 2 step (iv) as a yellow solid.
- 25 ¹H NMR δ (d₆-DMSO): 12.75(bs,1H), 8.07(bs,1H), 7.61(d, 1H), 7.31(t, 1H), 7.25(d, 1H), 7.09(d, 1H), 7.02(bs, 1H), 6.96(dd, 1H), 6.88(dd, 1H), 5.73(d, 1H), 5.49(d, 1H), 5.15(t, 1H), 5.10(d, 1H), 4.04(q, 1 H), 3.96(q, 1H), 3.90-3.85(m, 1H), 3.8(bs, 2H), 3.7-3.6(m, 1H), 3.55-3.45(m, 1H)
- 30 (v) The tetrasodium salt of the monoanhydride of 5-(3-(3,4-dichlorophenoxy)-phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iii) as a yellow powder.
- 35 ³¹P NMR δ (D₂O): 10.12(d), 3.97(dd), -9.2(d);
- MS: ESI-loop: 815/819/821

Example 16

Tetrasodium salt of the monoanhydride of 5-(3-(4-methoxyphenoxy)phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

5

(i) 5-(Hydroxy-(3-((4-methoxyphenoxy)phenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine according to the method of Example 1 step (i) (using 3-(4-methoxyphenoxy)benzaldehyde instead of benzophenone) as a colourless foam.

10 $^1\text{H NMR } \delta$ (CDCl_3): 8.26(bs, 1H), 7.38(d, 1H), 6.7-7.1(m, 7H), 5.9-5.86(m, 1H), 5.49-5.46(m, 1H), 4.57(bs, 1H), 4.05-4.00(m, 1H), 4.95-4.90(m, 2H), 3.73(s, 3H), 3.7-3.5(m, 2H), 3.9-3.8(m, 1H), 0.86(s, 9H), 0.83(s, 9H), 0.73(s, 9H), -0.2-0.05(s, 18H)

(ii) 5-(3-(4-Methoxyphenoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 2 step (ii) as a colourless foam.

$^1\text{H NMR } \delta$ (CDCl_3): 8.21 (bs, 1H), 7.31(s, 1H), 7.09(t, 1H), 6.7-6.9(m, 6H), 6.66(dd, 1H), 5.89(d, 1H), 4.05(m, 1H), 3.9(m, 2H), 3.7(s, 3H), 3.68(dd, 1H), 3.58(dd, 1H), 3.55(m, 2H), 0.82(m, 18H), 0.78(s, 9H), -0.2-0.05(m, 18H)

20

(iii) 5-(3-(4-Methoxyphenoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam.

25 $^1\text{H NMR } \delta$ (CDCl_3): 9.29(bs, 1H), 7.3(s, 1H), 7.11(t, 1H), 6.75-6.9(m, 6H), 6.69(dd, 1H), 5.85(d, 1H), 4.03(m, 1H), 3.98(m, 2H), 3.83(d, 1H), 3.76(d, 1H), 3.72(s, 3H), 3.66(dd, 1H), 3.56(dd, 1H), 0.84(s, 9H), 0.82(s, 9H), 0.79(s, 9H), -0.2-0.05(m, 18H)

(iv) 5-(3-(4-Methoxyphenoxy)phenylmethyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 2 step (iv) as a yellow solid.

30 $^1\text{H NMR } \delta$ (CDCl_3): 11.13(bs, 1H), 7.26(s, 1H), 7.15(t, 1H), 6.75-7.0(m, 6H), 6.78(dd, 1H), 5.70(d, 1H), 4.78(bs, 1H), 4.30-4.25(m, 1H), 4.25-4.15(m, 2H), 4.07(m, 1H), 3.8-3.5(m, 4H), 3.75(s, 3H)

(v) The tetrasodium salt of the monoanhydride of 5-(3-(4-methoxyphenoxy)phenylmethyl)-4-thiouridine-5'-phosphate with

35

dichloromethylenebisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iii).

^{31}P NMR δ (D_2O): 10.05(d), 3.95(dd), -9.27(d);

MS: ESI-loop: 777/779/781

5

Example 17

Tetrasodium salt of the monoanhydride of 5-((3-methoxy-4-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

10

(i) 5-(Hydroxy-((3-methoxy-4-phenylmethoxy)phenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using 3-methoxy-4-phenylmethoxybenzaldehyde instead of benzophenone) as a colourless foam.

15

^1H NMR δ (CDCl_3): 8.3(bs, 1H), 7.2-7.45(m, 6H), 6.94(bs, 1H), 6.85-6.75(m, 2H), 5.45(d, 1H), 5.07(s, 2H), 4.03(m, 1H), 3.6-3.55(m, 1H), 3.24(d, 1H), 0.82(s, 9H), 0.81(s, 9H), 0.76(s, 9H), -0.15-0.01(m, 18H)

20

(ii) 5-((3-Methoxy-4-phenylmethoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 2 step (ii) as a colourless foam.

^1H NMR δ (CDCl_3): 8.27(bs, 1H), 7.2-7.4(m, 6H), 6.71(d, 1H), 6.67(d, 1H), 6.54(dd, 1H), 5.86(d, 1H), 5.02(s, 2H), 4.03(m, 2H), 3.98(m, 2H), 3.76(s, 3 H), 3.71(dd, 1H), 3.64(dd, 1H), 3.46(d, 1H), 3.51(d, 1 H), 0.82(s, 9H), 0.81(s, 9H) 0.75(s, 9H), -0.2-0.0(m, 18H)

25

(iii) 5-((3-Methoxy-4-phenylmethoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam.

^1H NMR δ (CDCl_3): 9.31(bs, 1H), 7.36(d, 2H), 7.25-7.35(m, 3H), 7.23(d, 1H), 6.76(d, 1H), 6.70(d, 1H), 6.54(dd, 1H), 5.83(d, 1H), 5.05(s, 1H), 4.07(m 1H), 3.97(m, 2H), 3.79(s, 3H), 3.78(m, 1H), 3.71(dd, 1H), 3.6(dd, 1H), 0.84(s, 9H), 0.83(s, 9H), 0.79(s, 9H), -0.2-0.05(m, 18H)

35

(iv) 5-((3-Methoxy-4-phenylmethoxy)phenylmethyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 2 step (iv) as a yellow solid.

¹H NMR δ (CDCl₃): 11.09(bs, 1H), 7.25-7.5(m, 5H), 7.14(s, 1H), 6.72-6.68(m, 2H)
6.65(d, 1H), 5.66(d, 1H), 5.07(s, 2H), 4.67(bs, 1H), 4.23(m, 1H), 4.07(m, 2H), 3.99(s, 1H),
3.81(s, 3H), 3.75-3.65(m, 2H), 3.6-3.4(m, 2H)

- 5 (v) The tetrasodium salt of the monoanhydride of 5-((3-methoxy-4-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iii) as a yellow powder.

³¹P NMR δ (D₂O): 9.25(d), 1.75(dd), -9.66(d);

10 MS: FAB: 881 (M+1)

Example 18

Tetrasodium salt of the monoanhydride of 5-((4-methoxy-3-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

15

- (i) 5-(Hydroxy((4-methoxy-3-phenylmethoxy)phenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine according to the method of Example 1 step (i) (using 4-methoxy-3-phenylmethoxybenzaldehyde instead of benzophenone) as a colourless foam.

20

MS: FAB(-ve): 827(M-1)

- (ii) 5((4-Methoxy-3-phenylmethoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 2 step (ii) as colourless foam.

25

¹H NMR δ (CDCl₃): 8.49(s, 1H), 7.36-7.16(m, 6H), 6.73-6.62(m, 3H), 5.86(d, 1H), 5.00(s, 2H), 4.04(m, 1H), 3.93(m, 2H), 3.74(s, 3H), 3.74-3.58(s, 2H), 3.45(s, 2H), 0.86-0.75(m, 27H), 0.0-0.16(m, 18H)

- 30 (iii) 5((4-Methoxy-3-phenylmethoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam.

MS: FAB(-ve): 827(M-1)

- 35 (iv) 5-((4-Methoxy-3-phenylmethoxy)phenylmethyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 4 step (iv) as a yellow solid.

MS: FAB(+ve): 487(M+1)

(v) The tetrasodium salt of the monoanhydride of 5-((4-methoxy-3-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-phosphate with

- 5 dichloromethylenebisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iii) as a yellow powder.

^{31}P NMR δ (D_2O): 9.55(d), 2.66(dd), -9.60(d);

MS: ESI-loop: 791/793/795(M-1)

10 **Example 19**

Tetrasodium salt of the monoanhydride of 5-(4-butoxyphenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

- (i) 5-((4-Butoxyphenyl)hydroxymethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2', 3', 5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using 4-butoxybenzaldehyde instead of benzophenone) as a colourless foam.

^1H NMR δ (CDCl_3): 8.26(s, 1H), 7.36(s, 1H), 7.2(d, 1H), 6.80(d, 1H), 5.88(d, 1H), 5.49(d, 1H), 4.00(m, 1H), 3.93(m, 2H), 3.66(dd, 1H), 3.55(dd, 1H), 3.26(d, 1H), 1.67(m, 2H),
20 1.40(m, 2H), 0.80(m, 30H), 0.00(m, 18H)

(ii) 5-(4-Butoxyphenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 2 step (ii) as a pale yellow foam.

25 ^1H NMR δ (CDCl_3): 7.94(s, 1H), 7.16(s, 1H), 7.0(d, 2H), 6.7(d, 2H), 5.83(d, 1H), 4.0(m, 1H), 3.93(m, 2H), 3.82(t, 2H), 3.6(dd, 1H), 3.47(d, 1H), 1.63(m, 2H), 1.34-1.41(m, 2H), 0.73-0.88(m, 30H), -0.15-0.00(m, 18H)

- (iii) 5-(4-Butoxyphenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam.

^1H NMR δ (CDCl_3): 9.31(s, 1H), 7.19(s, 1H), 7.0(d, 2H), 6.73(d, 2H), 5.84(d, 1H), 4.02(m, 1H), 3.95(m, 1H), 3.90(m, 1H), 3.85(t, 2H), 3.76(d, 1H), 3.66(m, 1H), 3.56(m, 1H), 1.67(m, 2H), 1.38(m, 2H), 0.9(t, 3H), 0.83(m, 27H), -0.08-0.08 (m, 18H)

(iv) 5-(4-Butoxyphenylmethyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 2 step (iv) as a yellow solid.

MS: FAB: (+ve): 423(M+1)

- 5 (v) The tetrasodium salt of the monoanhydride of 5-(4-butoxyphenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iii) as a yellow powder.

^{31}P NMR δ (D_2O): 9.80(d), 3.66(dd), -9.5(d);

MS: ESI-loop: 363 (M) $^{2-}$

10

Example 20

Tetrasodium salt of the monoanhydride of 5-(9-ethylcarbazol-3-ylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

- 15 (i) 5-((9-Ethylcarbazol-3-yl)hydroxymethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using 9-ethyl-3-carbazolecarboxaldehyde instead of benzophenone) as a yellow foam.
- ^1H NMR δ (CDCl_3): 8.4(d, 1H), 8.10(m, 2H), 7.4(m, 5H), 7.2(t, 2H), 5.95(t, 1H), 5.83(m, 1H), 4.35(q, 2H), 4.17(m, 1H), 4.00(m, 2H), 3.60(m, 2H), 3.28-3.43(dd, 1H), 1.43(m, 3H)
- 20

(ii) The product of step (i) (15.83g) was subjected to hydrogenolysis at 2.5 atmospheres in ethanol (200ml) using 10% palladium on charcoal (1g) until reaction was complete by thin layer chromatographical analysis. The catalyst was filtered and the mother liquor collected.

- 25 The solvent was removed under reduced pressure. The remaining residue was purified by flash silica-gel chromatography to afford 5-(9-ethylcarbazol-3-ylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine as a yellow foam.

MS: FAB(-ve): 792(M-1)

- 30 (iii) 5-(9-Ethylcarbazol-3-ylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 2 step (iii) as a yellow foam.

^1H NMR δ (CDCl_3): 9.49(s, 1H), 8.05(d, 1H), 7.93(s, 1H), 7.49(t, 1H), 7.40(d, 1H), 7.34(m, 3H), 7.20(t, 1H), 5.91(m, 1H), 4.35(q, 2H), 4.11(m, 2H), 4.09(m, 1H), 4.01(m, 1H), 3.96(m, 1H), 3.68(dd, 1H), 3.58(dd, 1H), 1.28(t, 3H), 0.83-0.96(m, 27H), 0.00-0.15(m, 18H).

35

(iv) 5-(9-Ethylcarbazol-3-ylmethyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 2 step (iv) as a yellow solid.

MS: FAB(+ve): 468(M+1)

5

(v) The tetrasodium salt of the monoanhydride of 5-(9-ethylcarbazol-3-ylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (iv) according to the method of Example 1 step (iii) as a yellow powder.

³¹P NMR δ (D₂O): 9.65(d), 3.0(dd), -9.45(d);

10 MS: FAB(+ve): 840/842/844(M+1)

Example 21

Tetrasodium salt of the monoanhydride of 5-((4-phenyl)phenylthio)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid.

15

(i) 5-((4-Phenyl)phenylthio)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using (4-phenyl)phenyldisulphide (J. Chem. Soc. Perkin Trans. I 1983, (11), 2605-2609) instead of benzophenone) as a colourless foam.

20 MS: FAB(+ve): 771(M+1)

(ii) 5-((4-Phenyl)phenylthio)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (i) according to the method of Example 2 step (iii) as a yellow foam.

25 MS: FAB(+ve): 787(M+1)

(iii) 5((4-Phenyl)phenylthio)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 6 step (iv) as a yellow foam.

MS: FAB(+ve): 445(M+1)

30

(v) The tetrasodium salt of the monoanhydride of 5-((4-Phenyl)phenylthio)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (iii) according to the method of Example 1 step (iii) as a yellow powder.

³¹P NMR δ (D₂O): 9.60(d), 2.71(dd), -9.30(d);

35 MS: ESI-loop: 749/751/753

Example 22

Tetrasodium salt of the monoanhydride of 5-(9-methoxyfluoren-9-yl)uridine-5'-phosphate with dichloromethylenebisphosphonic acid.

- 5 (i) The product of Example 2 step (i) (10g) was dissolved in dry 1,2-dichloroethane (60ml) and treated with methanol (5.2ml) and 1M zinc dichloride solution in diethyl ether (100ml) at room temperature. After 16 hours the mixture was concentrated to about 15ml and 1,2-dichloroethane (40ml) was added. After stirring for 3 hours ethyl acetate (300ml) and water (50ml) was added. The organic phase was collected and again washed with water
10 (50ml). The organic phase was dried over magnesium sulphate and the solvent removed under reduced pressure. The residue was purified by flash silica-gel chromatography to afford 5-(9-methoxyfluoren-9-yl)-2',3',-bis-O-((1,1-dimethylethyl)dimethylsilyl)uridine as a colourless foam (5.8g).

¹H NMR δ (CDCl₃): 7.96(s, 1H), 7.63(bs, 1H), 7.54(d, 2H), 7.2-7.5(m, 2H), 7.10(m, 4H),
15 5.35(d, 1H), 4.66(dd, 1H), 4.09(dd, 1H), 3.97(bs, 1H), 3.74(d, 1H), 3.55(t, 1H), 3.37(dd, 1H), 2.64(s, 3H), 0.79(s, 9H), 0.82(s, 9H), -0.1-0.05(s, 12H)

(ii) 5-(9-Methoxyfluoren-9-yl)uridine was prepared from the product of step (i) according to the method of Example 2 step (iv) as a colourless foam.

20 ¹H NMR δ (d₆-DMSO): 11.06(bs, 1H), 8.4(s, 1H), 7.9(d, 2H), 7.35-7.45(m, 2H), 7.2-7.3(m, 4H), 5.88(d, 1H), 5.46(d, 1H), 5.16(d, 1H), 5.04(t, 1H), 4.17(q, 1H), 4.03(m, 1H), 3.93(m, 1H), 3.70(m, 1H), 3.60(m, 1H), 2.61(s, 3H)

(iii) The tetrasodium salt of the monoanhydride of 5-(9-methoxyfluoren-9-yl)uridine-5' phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (ii) according to the method of Example 1 step (iii) as a white powder.

³¹P NMR δ (D₂O): 9.70(d), 3.60(dd), -9.40(d);

MS: FAB(+ve): 811/813/815(M+1)

30 **Example 23**

Tetrasodium salt of 5-((4-phenyl)phenylcarbonyl)uridine-5'-phosphate, monoanhydride with dichloromethylenebisphosphonic acid.

(i) 5-((4-Phenyl)phenylcarbonyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine
35 was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to

the method of Example 1 step (i) (using (4-phenyl)phenylcarbonyl chloride instead of benzophenone) as a colourless foam.

¹H NMR δ (CDCl₃): 8.22(s, 1H), 8.21(s, 1H), 7.82(dd, 2H), 7.63(dd, 2H), 7.60(d, 2H), 7.40(m, 3H), 6.09(d, 1H), 4.18(m, 1H), 4.03(m, 2H), 3.83(dd, 1H), 3.69(dd, 1H), 0.93(s, 9H), 0.89(s, 9H), 0.8(s, 9H), -0.05-0.1 (m, 18H).

(ii) 5-((4-Phenyl)phenylcarbonyl)uridine was prepared from the product of step (i) according to the method of Example 2 step (iv) as a colourless foam.

¹H NMR δ (d₆-DMSO): 11.67(s, 1H), 8.56(s, 1H), 7.85(d, 2H), 7.78(d, 2H), 7.75(d, 2H), 7.51(t, 2H), 7.43(t, 1H), 5.82(d, 1H), 5.50(d, 1H), 5.11(d, 1H), 5.05(t, 1H), 4.12(q, 1H), 4.0(dd, 1H), 3.90(m, 1H), 3.63(m, 1H), 3.50(m, 1H).

(iii) The tetrasodium salt of the monoanhydride of 5-((4-phenyl)phenylcarbonyl)uridine-5'-phosphate with dichloromethylenebisphosphonic acid was prepared from the product of step (ii) according to the method of Example 1 step (iii) as a white powder.

³¹P NMR δ (D₂O): 9.9(d), 3.8(dd), -9.15(d);

MS: ESI-loop: 729(M-H)

Example 24

20 **Trisodium salt of 5-diphenylmethyluridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester.**

(i) 5-diphenylmethyluridine was prepared according to the method of Example 1 steps (i) and (ii) as a white solid (4g).

25 MS: FAB: m/e 411 (M+1)⁺

(ii) The product of step (i) (2.0g) and 1,8-bis(dimethylamino)naphthalene (1.7g) were dissolved in dry trimethylphosphate (20ml) and cooled to 0°C under a nitrogen atmosphere. Phosphorous oxychloride (0.55ml) was added dropwise and the resulting mixture stirred at low temperature for 3 hours before addition of bis(tri-n-butylammonium)pyrophosphate (50ml of a 0.5M solution in dimethylformamide) and tri-n-butylamine (5.1ml). After 5 minutes the reaction was quenched by addition of aqueous triethylammonium bicarbonate solution (300ml of a 0.2M solution) and stirred for 15 minutes before being extracted three times with ethyl acetate (100ml). The aqueous phase was concentrated under reduced pressure and the residue purified by reverse phase chromatography (C-18 Sep-pak silica) eluting with water. Fractions containing product were pooled and lyophilised to leave 5-

diphenylmethyluridine-5'-triphosphate tetrakis triethylammonium salt as a colourless gum (2.0g).

^{31}P NMR: δ (D_2O): -4.8(d), -9.7(d), -21.0(t);

- 5 (iii) The product of step (ii) (2.0g) was dissolved in dry pyridine (30ml) and concentrated to dryness under reduced pressure three times and then dissolved in dry pyridine (20ml) and tri-n-octylamine (1.7ml) and again was evaporated to dryness under reduced pressure. The resulting gum was slurried in dry 1,4-dioxane (30ml) under a nitrogen atmosphere and treated with tri-n-butylamine (0.9ml) and diphenylphosphochloridate (0.6ml) with further
10 stirring at room temperature for 2.5 hours. The solvents were evaporated under reduced pressure. Dry diethyl ether (50ml) and iso-hexane (200ml) were added and the mixture cooled to 0°C under nitrogen atmosphere with stirring for 30 minutes. The supernatant was decanted and the remaining gum dissolved in 1,4-dioxane (10ml) and evaporated to dryness under reduced pressure. The resulting gum was dissolved in dry pyridine (20ml)
15 under a nitrogen atmosphere and treated with dry methanol (10ml) and the resulting solution allowed to stir at room temperature for 2.5 hours. The volatiles were removed by evaporation under reduced pressure and the remaining residue partitioned between water (50ml) and diethyl ether (50ml). The aqueous phase containing the product was purified by reverse phase chromatography (C-18 Sep-pak silica) eluting with water. Fractions
20 containing product were pooled, lyophilised and the residue was dissolved in water and passed down an ion-exchange column (Dowex-50 Na^+ form) eluting with water. UV (254nm) active fractions were pooled, lyophilised and the residue was purified by reverse phase chromatography (C18 Sep-pak silica) eluting with water. Fractions containing product were pooled and lyophilised to leave 5-diphenylmethyluridine-5'-(tetrahydrogen
25 triphosphate) - P^3 - monomethyl ester, trisodium salt as a white powder (0.07g).

^{31}P NMR δ (D_2O): -7.95(d), -10.0(d), -21.4(t);

MS: (FAB) (+ve): m/e 731 ($\text{M}+\text{H}$) $^+$

Example 25

- 30 **Trisodium salt of 5-diphenylmethyluridine-5'-(tetrahydrogen-triphosphate)- P^3 -mono(n-propyl) ester.**

- (i) The product of Example 24, step (ii) (which was 5-diphenylmethyluridine-5'-triphosphate tetrakis triethylammonium salt) (2.35g) was dissolved in dry pyridine (50ml)
35 and concentrated to dryness under reduced pressure three times and then dissolved in dry pyridine (50ml) and tri-n-octylamine (1.95ml) and again this was evaporated to dryness

under reduced pressure. The resulting gum was slurried in dry 1,4-dioxane (40ml) under a nitrogen atmosphere and treated with tri-n-butylamine (1.06ml) and diphenyl-phosphochloridate (0.693ml) with further stirring at room temperature for 2.5 hours. The solvents were evaporated under reduced pressure. Dry diethyl ether (50ml) and iso-hexane (150ml) were added and the mixture stirred under a nitrogen atmosphere for 5 minutes. The supernatant was decanted and the remaining gum dissolved in dry pyridine (40ml).

(ii) 20ml of this solution was removed by dry syringe and added to a round bottom flask under nitrogen containing dry n-propanol (10ml). The mixture was stirred at room temperature for a further 16 hours before removing the solvent under reduced pressure and partitioning the residue between ether and water. The aqueous phase was separated and lyophilised. The resulting residue was purified by reverse phase chromatography (C-18 Sep-pak silica) eluting with water. Fractions containing product were pooled, lyophilised and the residue was dissolved in water and passed down an ion-exchange column (Dowex-50 Na⁺ form) eluting with water. The UV (254 nm) active fractions were pooled, lyophilised and the residue was purified by reverse phase chromatography (C18 Sep-pak silica) eluting with water. The fractions which contained the product were pooled and lyophilised to leave the trisodium salt of 5-diphenylmethyluridine-5'-(tetrahydrogen-triphosphate)-P³-mono(n-propyl) ester as a white solid (0.09g).
³¹P NMR δ (D₂O): -9.40(d), -10.34(d), - 21.74(t);
MS: ESI (-ve): 691 (M-3Na⁺+2H)

Example 26

Trisodium salt of 5-diphenylmethyluridine-5'-(tetrahydrogen-triphosphate)-P³-mono(2-methoxyethyl) ester.

20ml of the solution which was the product of step (i) of Example 25 was removed by dry syringe and added under nitrogen to a round bottom flask containing dry 2-methoxy ethanol (10ml). The mixture was stirred at room temperature for a further 16 hours before removing the solvent under reduced pressure and partitioning the residue between ether and water. The aqueous layer was separated and lyophilised. The resulting residue was purified by reverse phase chromatography (C-18 Sep-pak silica) eluting with water. Fractions containing the product were pooled, lyophilised and the residue was dissolved in water and passed down an ion-exchange column (Dowex-50 Na⁺ form) eluting with water. The UV (254 nm) active fractions were pooled, lyophilised and the residue was purified by reverse phase chromatography (C18 Sep-pak silica) eluting with water. The fractions which

contained the product were pooled and lyophilised to leave the trisodium salt of 5-diphenylmethyluridine 5'-(tetrahydrogen triphosphate) -P³ - mono(2-methoxyethyl) ester as a white powder (0.053g).

³¹P NMR δ (D₂O): -9.56(d), -10.23(d), -21.60(t);

5 MS: ESI (-ve): 707 (M-3Na⁺ +2H)

Example 27

Trisodium salt of 5-diphenylmethyluridine-5'-(tetrahydrogen-triphosphate)-P³-monophenylmethyl ester.

10

The product of Example 24, step (ii) (which was 5-diphenylmethyluridine-5'-triphosphate-tetrakis triethylammonium salt), (0.58g) was dissolved in dry pyridine (30ml) and concentrated to dryness under reduced pressure three times and then dissolved in dry pyridine (30ml) and tri-n-octylamine (0.48ml) and again was evaporated to dryness under
15 reduced pressure. The resulting gum was slurried in dry 1,4-dioxane (15ml) under a nitrogen atmosphere and treated with tri-n-butylamine(0.26ml) and diphenyl-phosphochloridate (0.171ml) with further stirring at room temperature for 2.5 hours. The solvents were evaporated under reduced pressure. Dry diethyl ether (50ml) and iso-hexane (150ml) were added and the mixture stirred under a nitrogen atmosphere for 2 minutes. The
20 supernatant was decanted and the remaining gum dissolved in dry pyridine (15ml) and treated with phenylmethyl alcohol (7ml). The mixture was stirred at room temperature for a further 16 hours before removing the solvent under reduced pressure and partitioning the residue between ether and water. The aqueous phase was separated and lyophilised. The resulting residue was purified by reverse phase chromatography (C-18 Sep-pak silica)
25 eluting with 0.1M aqueous triethylammonium bicarbonate solution. Fractions containing product were pooled, lyophilised and the residue was dissolved in water and passed down a ion-exchange column (Dowex-50 Na⁺ form) eluting with water. The UV (254 nm) active fractions were pooled, lyophilised and the residue was purified by reverse phase chromatography (C18 Sep-pak silica) eluting with water. The fractions which contained
30 the product were pooled and lyophilised to leave the trisodium salt of 5-diphenylmethyluridine 5'-(tetrahydrogen triphosphate) -P³ - monophenylmethyl ester as a white solid (0.031g).

³¹P NMR δ (D₂O): -9.62(d), -10.00(d), -21.44(t);

MS: ESI (loop): 739 (M-3Na⁺ +2H)

35

Example 28**Trisodium salt of 5-diphenylmethyl-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester.**

- 5 (i) The product of Example 1 step (i), (5-(hydroxy-(1,1-diphenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine) (6.8g), was dissolved in dichloromethane (80ml) and triethylsilane (1.83ml) and treated with trifluoroacetic acid (1.38ml). After stirring for 20 minutes the solvents were removed under reduced pressure and any remaining traces removed by azeotroping three times with toluene. The remaining residue was dissolved in
10 dimethylformamide (5ml) and treated with imidazole (0.54g) and t-butyltrimethylsilylchloride (0.6g). After stirring for 16 hours the mixture was partitioned between water and iso-hexane and the organic phase was washed with water, collected and dried over magnesium sulphate. The solvent was removed under reduced pressure and the residue was purified by flash silica-gel chromatography eluting with ethyl acetate/iso-hexane mixtures
15 to afford 5-diphenylmethyl-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine as a colourless foam (5.94g)
¹HNMR δ (CDCl₃): 8.49(bs, 1H), 7.35-7.0(m, 11H), 6.68(s, 1H), 5.76(d, 1H), 5.41(s, 1H), 3.87(m, 2H), 3.73(m, 1H), 3.29(dd, 1H), 3.21(dd, 1H), 0.85(m, 27H), 0.00(m, 18H).
- 20 (ii) The product of step (i) (6.9g) was dissolved in dry pyridine (180ml) under a atmosphere of nitrogen and treated with phosphorous pentasulphide (10.16g) before refluxing for 20 hours. The solvent was removed under reduced pressure and the residue was partitioned between a saturated sodium bicarbonate solution and ethyl acetate. The organic phase was collected and solvent was removed under reduced pressure. The residue
25 was purified by flash silica-gel chromatography eluting with ethyl acetate/iso-hexane mixtures to afford 5-diphenylmethyl-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine as a yellow foam (5.5g).
MS: ESI+loop: 770(M+1)
- 30 (iii) The product of step (ii) (5.5g) was treated with 1M tetra-n-butylammonium fluoride in tetrahydrofuran (21.5ml) at room temperature. After stirring for 2 hours the solvent was removed under reduced pressure and the residue was purified by flash silica-gel chromatography eluting with ethyl acetate/iso-hexane mixtures to afford 5-diphenylmethyl-4-thiouridine as a yellow solid (1.3g).
35 MS: EI: 426(M⁺)

(iv) The trisodium salt of 5-diphenylmethyl-4-thiouridine -5'-(tetrahydrogen triphosphate) -P³-monomethyl ester was prepared from the product of step (iii) according to the method of Example 24 steps (ii) and (iii).

³¹P NMR δ (D₂O): -8.02(d), -10.15(d), -21.39(t);

5 MS: ESI+loop: 745(M+1)

Example 29

Triammonium salt of 5-(1,1-bis(4-methoxyphenyl)methyl)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester.

10

(i) 5-(Hydroxy-1,1-bis(4-methoxyphenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (but using 4,4'-dimethoxybenzophenone instead of benzophenone).

15 MS: FAB: m/e 811 (M+H-H₂O)⁺

(ii) The product of step (i) (3.8g) was dissolved in dichloromethane (75 ml) and triethylsilane (0.8ml) and was treated with trifluoroacetic acid(3.59ml). After stirring for 1 hour at room temperature, the volatiles were removed under reduced pressure and any remaining traces removed by azeotroping four times with toluene. The residue was treated with 1M tetra-n-butylammonium fluoride solution in tetrahydrofuran (15ml). After stirring for 36 hours, the solvent was removed under reduced pressure and the residue was purified by silica-gel chromatography eluting with 2% methanol in ethyl acetate to afford 5-(1,1-bis(4-methoxyphenyl)methyl)uridine as a white solid (1.4g).

25 MS: FAB(+ve): m/e 471 (M+H)⁺

(iii) The triammonium salt of 5-(1,1-bis(4-methoxyphenyl)methyl)uridine 5'-(tetrahydrogen triphosphate) P³-monomethyl ester was prepared from the product of step (ii) according to the method of Example 24 steps (ii) and (iii), with further purification by reverse phase HPLC eluting with 10% methanol in 0.1% aqueous ammonium acetate solution, and obtained as a white solid.

30

³¹P NMR: δ (D₂O): -8.1(d), -10.2(d), -21.6(t);

MS: ESI-loop: 723(M-H)

Example 30

Diammonium salt of 5-(1,1-bis(4-methoxyphenyl)methyl)-4-thiouridine-5'-(tetrahydrogen triphosphate)-P³-monomethyl ester.

- 5 (i) The product of Example 29 step (i) (3.93g) was dissolved in dichloromethane (70ml), triethylsilane (0.83ml) and cooled to 0°C. The mixture was treated with boron trifluoride diethyl etherate (2.34ml) in small portions. After 30min the mixture was quenched with cold saturated sodium bicarbonate solution. The organic phase was collected, the solvent was evaporated under reduced pressure and the product was azeotroped with toluene. The residue was dissolved in dimethylformamide (20ml) and treated with imidazole (1.28g) and t-butyltrimethylsilylchloride (1.43g) for 72 hours. The reaction mixture was quenched with water and extracted three times with iso-hexane. The organic phase was washed with water, collected, dried over magnesium sulphate and the solvent was evaporated under reduced pressure to give 5-(1,1-bis(4-methoxyphenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine as a yellow oil (3.9g).

MS: FAB(+ve)m/e: 813(M+1), FAB(-ve)m/e: 811(M-1).

- (ii) 5-(1,1-bis(4-methoxyphenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (i) according to the method of Example 28 step (ii) as a yellow foam.

MS: FAB(-ve)m/e: 827(M-1)

- (iii) 5-(1,1-bis(4-methoxyphenyl)methyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 28 step (iii) as a yellow solid.

MS: APCI: m/e: 487(M+1)

- (iv) The diammonium salt of 5-(1,1-bis(4-methoxyphenyl)methyl)-4-thiouridine 5'-(tetrahydrogen triphosphate) P³-monomethyl ester was prepared from the product of step (iii) according to the method of Example 24 steps (ii) and (iii), purified by reverse phase HPLC eluting with 10% methanol in 0.1% aqueous ammonium acetate solution, and obtained as a yellow solid.

³¹P NMR: δ (D₂O): -8.3(d), -10.3(d), -21.4(t);

MS: ESI(-ve)m/e: 739(M-H)

Example 31

Tri-n-butylammonium salt of 5-(1,1-bis(4-methoxyphenyl)methyl)-4-thiouridine-5'-(dihydrogen-phosphate)-monomethyl ester

- 5 Obtained as a yellow solid from the products of Example 30 step (iv) by reverse phase HPLC purification of the final reaction mixture eluting with 10-50% aqueous methanol.
 ^{31}P NMR: δ (D_2O): 2.86(s)
MS: (FAB)(-ve): 579(M-1)

10 **Example 32**

Trisodium salt of 5-(9H-fluoren-9-yl)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester.

- 15 (i) 5-(9-Hydroxyfluoren-9-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using 9-fluorenone instead of benzophenone) as a colourless foam.
MS: FAB: m/e: 854/852(M+Rb)

- 20 (ii) The product of step (i) (6.56g) was treated with a 1M solution of tetra-n-butyl ammonium fluoride in tetrahydrofuran (28.2ml) and the mixture was stirred at room temperature for 16 hours. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica-gel eluting with 10% methanol in ethyl acetate to give 5-(9-hydroxyfluoren-9-yl)uridine as a pale yellow solid (3.43g).
25 MS: FAB: m/e: 425(M+1)

- (iii) The product of step (ii) (3.37g) was dissolved in dichloromethane (100ml) and triethylsilane (1.39ml) and treated with trifluoroacetic acid (6.23ml). The mixture was stirred at room temperature for 36 hours. The solvent was evaporated under reduced
30 pressure and the residue azeotroped three times with toluene. The remaining residue was purified by flash chromatography on silica-gel eluting with 15% methanol in ethyl acetate to give 5-(9H-fluoren-9-yl)uridine as white powder (1.09g).
MS: FAB: m/e: 409(M+1)

(iv) The trisodium salt of 5-(9H-fluoren-9-yl)uridine 5'-(tetrahydrogen triphosphate) P^3 - monomethyl was prepared as a white powder from the product of step (iii) according to the method of Example 24 steps (ii) and (iii).

^{31}P NMR: δ (D_2O): -8.38(d), -10.46(d), -21.85(t);

5 MS: ESI-loop: m/e: 661(M-H)

Example 33

Disodium salt of 5-(9H-fluoren-9-yl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)- P^3 -monomethyl ester,

10

(i) 5-(9H-fluoren-9-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of Example 32 step (i) according to the method of Example 30 step (i) as a colourless foam and used directly in the next step.

15 (ii) 5-(9H-fluoren-9-yl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (i) according to the method of Example 28 step (ii) as a yellow foam.

MS: FAB(-ve): m/e: 765(M-1)

20 (iii) 5-(9H-fluoren-9-yl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 32 step (iii) as a yellow solid.

MS: EI: 424(M^+)

25 (iv) The disodium salt of 5-(9H-fluoren-9-yl)-4-thiouridine 5'-(tetrahydrogen triphosphate) P^3 - monomethyl ester was prepared from the product of step (iii) according to the method of Example 24 steps (ii) and (iii) as a yellow powder.

^{31}P NMR: δ (D_2O): -8.95(dx2), -11.0(dx2), -22.3(tx2); - rotamers

MS: FAB(+ve): 745(M+1)

30 Example 34

Diammonium salt of 5-(9H-fluoren-9-yl)-4-thiouridine 5'-(trihydrogen-diphosphate)- P^3 -monomethyl ester

35 Obtained as a yellow solid from the products of Example 33 step (iv) by HPLC purification of the final reaction mixture but eluting with 10-50% methanol in 0.1% aqueous ammonium acetate solution instead.

^{31}P NMR: δ (D_2O): -8.2(d), -10.1(d)

MS: (FAB)(-ve): 597(M-1)

Example 35

- 5 **Ammonium salt of 5-(9H-fluoren-9-yl)-4-thiouridine-5'-(dihydrogen-phosphate)-monomethyl ester**

Obtained from the products of Example 33 step (iv) by HPLC purification of the final reaction mixture as a yellow solid but eluting with 10-50% methanol in 0.1% aqueous ammonium acetate solution instead.

10 ^{31}P NMR: δ (D_2O): 3.08(s), 2.75(bs)-rotamers

MS: FAB(+ve): 519(M+1), FAB(-ve): 517(M-1)

Example 36

- 15 **Trisodium salt of 5-triphenylsilyluridine-5'-(tetrahydrogen-triphosphate)- P^3 -monomethyl ester.**

(i) 5-Triphenylsilyl-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared as a colourless foam from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using triphenylsilylchloride instead of benzophenone).

20 MS: FAB(+ve): 845(M+1)

(ii) 5-triphenylsilyluridine was prepared from the product of step (i) according to the method of Example 28 step (iii).

25 MS: FAB(+ve): 503(M+1)

(iii) The trisodium salt of 5-triphenylsilyluridine 5' (tetrahydrogen triphosphate) - P^3 - monomethyl ester was prepared from the product of step (ii) according to the method of Example 24 steps (ii) and (iii) as a white powder.

30 ^{31}P NMR: δ (D_2O): -8.12(d), -10.18(d), -21.55(t);

MS: (FAB): 823(M+1)

Example 37**Trisodium salt of 5-phenylthiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester.**

- 5 (i) 5-phenylthiouridine (2.0g) (for preparation see Tetrahedron Letters, (1987), 28, (1), 87-90) and 1,8-bis(dimethylamino)naphthalene (1.7g) in dry trimethylphosphate (30ml) were cooled to 0-5°C under a nitrogen atmosphere. Phosphorous oxychloride (0.64ml) was added dropwise and the resulting mixture stirred at low temperature for 3 hours before addition of bis(tributylammonium)pyrophosphate (50ml of a 0.5M solution in
10 dimethylformamide) and tri-n-butylamine (5.9ml). After 5 minutes the reaction was quenched by addition of aqueous triethylammonium bicarbonate solution (300ml of a 0.2M solution) and stirred for 15 minutes before being extracted three times with ethyl acetate (100ml). The aqueous phase was concentrated under reduced pressure to approximately 80ml and the residue purified by ion-exchange chromatography (DEAE Sephadex eluting
15 with 0 - 0.5M triethylammonium bicarbonate solution). The fractions containing the tetrakis triethylammonium salt of 5-phenylthiouridine 5'-triphosphate were pooled and lyophilised to leave a colourless gum (1.6g).
³¹P NMR: δ (D₂O): -4.8(d), -10.0(d), -21.0(t);

- 20 (ii) The product of step (i) (1.6g) was dissolved in dry pyridine (30ml) and concentrated to dryness under reduced pressure three times and then dissolved in dry pyridine (20ml) and tri-n-octylamine (1.4ml) and again this was evaporated to dryness under reduced pressure. The resulting gum was slurried in dry 1,4-dioxane (30ml) under a nitrogen atmosphere and then treated with tri-n-butylamine (0.77ml) and diphenylphosphochloridate (0.49ml) with
25 further stirring at room temperature for 2.5 hours. The solvents were then evaporated under reduced pressure. Dry diethyl ether (50ml) and iso-hexane (200ml) were added and the mixture was cooled to 0°C under nitrogen atmosphere with stirring for 30 minutes. The supernatant was decanted and the remaining gum dissolved in 1,4-dioxane (10ml) and then evaporated to dryness under reduced pressure. The resulting gum was dissolved in dry
30 pyridine (15ml) under a nitrogen atmosphere and treated with dry methanol (7.5ml) and the resulting solution was stirred at room temperature for 2.5 hours. The volatiles were then removed by evaporation under reduced pressure and the remaining residue partitioned between water (50ml) and diethyl ether (50ml). The aqueous phase containing the product was purified by reverse phase chromatography (C-18 Sep-pak silica, eluting with water).
35 The fractions containing the product were pooled and lyophilised and the residue was dissolved in water and passed down an ion-exchange column (Dowex-50 Na⁺ form). The

UV (254 nm) active fractions were pooled and lyophilised and the residue was purified by reverse phase chromatography (C18 Sep-pak silica, eluting with water). The fractions containing product were pooled and lyophilised to leave the trisodium salt of 5-phenylthiouridine 5'-(tetrahydrogen triphosphate) P^3 - monomethyl ester as a white powder (0.3g).
5 ^{31}P NMR δ (D_2O): -8.2 (d), -10.2 (d), -21.6 (t);
MS: m/e 673 ($\text{M}+\text{H}$)⁺

Example 38

10 **Trisodium salt of 5-ethyl-4-thiouridine-5'-(tetrahydrogen-triphosphate)- P^3 -monomethyl ester.**

(i) To a solution of 5-ethyl-2',3',5'-tris-O-benzoyluridine (0.58g) in pyridine (18ml) was added phosphorous pentasulphide (1.11g) and then water (1.5ml) dropwise. The resultant
15 solution was heated at reflux for 16 hours. After cooling to room temperature the reaction mixture was concentrated to two thirds volume under reduced pressure and then treated with water (200ml). After stirring for 1 hour the solid precipitate was filtered and dissolved in dichloromethane and again filtered. The mother liquor was collected, solvent removed under reduced pressure and the resulting solid filtered by washing three times with water
20 (20ml). The solid collected was further purified by silica-gel chromatography eluting with chloroform-methanol mixtures to leave 5-ethyl-2',3',5'-tris-O-benzoyl-4-thiouridine as a yellow solid (0.47g).
MS: m/e 601 ($\text{M}+\text{H}$)⁺.

25 (ii) Sodium hydride (0.1g) (60% dispersion in mineral oil) was added to dry methanol (50ml) under an atmosphere of nitrogen at 0°C. The product from step (i) (3.0g) was added to the above solution and the whole was refluxed for 2 hours. After cooling to room temperature, glacial acetic acid (0.28ml) was added and the volatiles were then removed under reduced pressure. The residue was dissolved in water (20ml) and then extracted
30 three times with diethyl ether (20ml). The aqueous phase was evaporated to dryness under reduced pressure. The resulting solid was triturated with acetone and filtered to leave 5-ethyl-4-thiouridine as a yellow solid (1.39g).
MS: m/e 289 ($\text{M}+\text{H}$)⁺.

(iii) The tri sodium salt of 5-ethyl-4-thiouridine 5'-(tetrahydrogen triphosphate) P^3 - monomethyl ester was prepared from the product of step (ii) according to the method of Example 37 steps (i) and (ii) as a yellow powder.

^{31}P NMR: δ (D_2O): -8.27(d), -10.44(d), -21.74(t);

5 MS: m/e 609 ($M+H$)⁺.

Example 39

Trisodium salt of 5-((4-methoxy)phenylthio)uridine-5'-(tetrahydrogen triphosphate)- P^3 -monomethyl ester.

10

(i) A suspension of dry lithium chloride (1.23g) and palladium dichloride (2.55g) was stirred under a nitrogen atmosphere in dry methanol for 14 hours forming a dark tan solution. 5-Chloromercuriuridine (3.44g) (see JOC 1991, 56, (19), 5598 for preparation) and (4-methoxy)phenyldisulphide (5.00g) were added and the mixture was stirred at room temperature for a further 14 hours. The mixture was saturated with hydrogen sulphide by bubbling the gas through the mixture for five minutes. The precipitate formed was filtered through celite and further washed with methanol. The mother liquor was absorbed onto silica-gel and subjected to flash chromatography eluting with 10% methanol in dichloromethane to give a white semi-solid upon evaporation of the product fractions. This was dissolved in methanol and filtered and again the solvent was removed *in vacuo* leaving 5-((4-methoxy)phenylthio)uridine as a white solid (2.43g).

15

MS: FAB: m/e 383 ($M+H$)⁺

(ii) The tetrakis triethylammonium salt of 5-((4-methoxy)phenylthio)uridine-5'-

25 triphosphate was prepared from the product of step (i) according to the method of Example 37 step (i) as a white powder.

^{31}P NMR: δ (D_2O): -6.46 (d), -10.17 (d), -21.40 (t).

(iii) The trisodium salt of 5-((4-methoxy)phenylthio)uridine-5'-(tetrahydrogen-

30 triphosphate)- P^3 -monomethyl ester was prepared from the product of step (ii) according to the method of Example 37 step (ii) as a white powder.

^{31}P NMR: δ (D_2O): -8.21 (d), -10.26 (d), -21.64 (t);

MS: m/e 635 ($M-3Na^++2H$)

Example 40

Trisodium salt of 5-((2-phenyl)phenylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester.

- 5 (i) To a solution of 2-bromo-biphenyl (10.6g) in dry THF (150ml) under an atmosphere of nitrogen at -78°C was added 53.5 ml of a 1.7M solution of t-butyllithium in pentane dropwise over 15 minutes using a dropping funnel. A deep yellow solution was formed. After 30 minutes the reaction mixture was allowed to reach and remain at room temperature for five minutes by removing the cooling bath. The reaction mixture was then cooled to approximately -10°C and quenched with solid sulphur (1.45g). The mixture was
10 then allowed to reach room temperature with further stirring for 1 hour. The mixture was carefully quenched with saturated aqueous ammonium chloride solution (100ml) and then extracted with diethyl ether. The aqueous phase was collected, acidified with 2M hydrochloric acid and extracted with diethyl ether. The organic phase was collected and the solvent removed *in vacuo* leaving the thiol as a colourless oil (7.8 g). The crude thiol
15 was dissolved in dimethylsulphoxide (4ml) and stirred at room temperature for 24 hours and then at 60-80°C for a further 24 hours. The cooled mixture was partitioned between diethyl ether and 1M sodium hydroxide solution. The organic phase was collected and the solvent was removed *in vacuo*. The resulting oil was purified by flash chromatography on silica-gel eluting with 10% diethyl ether in isohexane to give 2-(phenyl)phenyldisulphide
20 as a pale yellow gum (6.9 g).

¹H NMR: δ (CDCl₃): 7.2-7.6 (m, aromatics)

MS: ESI: m/e 370 (M+H)⁺

- 25 (ii) 5-((2-Phenyl)phenylthio)uridine was prepared from the product of step (i) and 5-chloromercuriuridine according to the method of Example 39 step (i) as a colourless solid.
MS: FAB (+ve): m/e 429 (M+H)⁺

- 30 (iii) The trisodium salt of 5-((2-phenyl)phenylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester was prepared from the product of step (ii) according to the method of Example 24 steps (ii) and (iii) as a colourless solid.

³¹P NMR: δ(D₂O): -7.95 (d), -10.04 (d), -21.24 (t);

MS: ESI (loop): 725 (M-3H+2Na⁺).

Example 41

Trisodium salt of 5-((3-phenyl)phenylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester.

- 5 (i) 3-(Phenyl)phenyldisulphide was prepared from 3-bromo-biphenyl according to the method of Example 40 step (i) as a white solid.

MS: ESI: m/e 370(M+H)⁺

- 10 (ii) 5-((3-Phenyl)phenylthio)uridine was prepared from the product of step (i) and 5-chloromercuriuridine according to the method of Example 40 step (ii) as a colourless solid.

MS: FAB (+ve): m/e 429(M+H)⁺

- 15 (iii) The trisodium salt of 5-((3-phenyl)phenylthio)uridine 5'-(tetrahydrogen triphosphate)-P³-monomethyl ester was prepared from the product of step (ii) according to the method of Example 24 steps (ii) and (iii) as a white powder.

³¹P NMR: δ (D₂O): -8.23(d), -10.21(d), -21.50(t);

MS: ESI (loop): 725 (M-3H+2Na⁺).

Example 42

- 20 **Trisodium salt of 5-((4-phenyl)phenylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester.**

- (i) 4-(Phenyl)phenyldisulphide (J. Chem. Soc. P1: 1987, (1), 187) was prepared from 4-bromo-biphenyl according to the method of Example 40 step (i) as a white solid.

25 MS: ESI: m/e 370(M+H)⁺

- (ii) 5-((4-Phenyl)phenylthio)uridine was prepared from the product of step (i) and 5-chloromercuriuridine according to the method of Example 40 step (ii) as a white solid.

MS: FAB (-ve): m/e 427(M-H)⁺

- 30 (iii) The trisodium salt of 5-((4-phenyl)phenylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester was prepared from the product of step (ii) according to the method of Example 24 steps (ii) and (iii) as a white powder.

³¹P NMR: δ (D₂O): -8.14(d), -10.17(d), -21.57(t);

35 MS:ESI (loop): 681 (M-3Na⁺-H).

Example 43

Triammonium salt of 5-(2-naphthylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester.

- 5 (i) 5-(2-Naphthylthio)uridine was prepared from 5-chloromercuriuridine and 2,2'-dinaphthyl disulphide (see Synth. Commun. 1985, 15, (1), 1 for preparation) according to the method of Example 40 step (ii).
MS: FAB: m/e 409 (M+Li)⁺
- 10 (ii) The triammonium salt of 5-(2-naphthylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester was prepared as a white solid from the product of step (i) according to the method of Example 24 steps (ii) and (iii), and purified by reverse phase HPLC using a 10-60% methanol in 0.5% aqueous ammonium acetate mixture as eluant.
³¹P NMR: δ (D₂O): -8.19(d), -10.22(d), -21.50(t)

15

Example 44

Trisodium salt of 5-((3-phenoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester.

- 20 (i) 5-(Hydroxy-((3-phenoxy)phenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using 3-phenoxybenzaldehyde instead of benzophenone) as a colourless foam.
MS: ESI(+ve): 785(M+1)
- 25 (ii) 5-((3-Phenoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 40 step (i) as a colourless foam.
MS: ESI(+ve): 769(M+1)
- 30 (iii) 5-((3-Phenoxy)phenylmethyl)-2',3',5' - tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 28 step (ii) as a yellow foam.
MS: FAB(-ve): 783(M-1)

35

- (iv) The product of step (iii) (3.5g) was dissolved in acetonitrile (70ml) and treated with a 1:1 hydrofluoric acid-pyridine complex (20ml). After 3 hours the mixture was quenched with saturated aqueous sodium carbonate solution (100ml) and the product extracted into ethyl acetate. The organic phase was collected, dried over magnesium sulphate and the solvent was removed under reduced pressure. The residue was purified by flash silica-gel chromatography eluting with chloroform-methanol mixtures to afford 5-((3-phenoxy)phenylmethyl)-4-thiouridine as a yellow powder (1.5g).
MS: FAB(+ve): 443(M+1), FAB(-ve): 441(M-1).
- (v) The trisodium salt of 5-((3-phenoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester was prepared from the product of step (iv) according to the method of Example 24 steps (ii) and (iii) as yellow powder.
³¹P NMR: δ (D₂O): -8.16(d), -10.35(d), -21.56(t);
MS: FAB: m/e 763 (M+H)⁺

Example 45

Trisodium salt of 5-((4-phenoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester.

- (i) 5-(Hydroxy-((4-phenoxy)phenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine according to the method of Example 1 step (i) (using 4-phenoxybenzaldehyde instead of benzophenone) as a colourless foam.
MS: FAB(+ve): 883(M+Rb)
- (ii) 5-((4-Phenoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 28 step (i) as a colourless foam.
MS: FAB(+ve): 769(M+1), 853(M+Rb).
- (iii) 5-((4-Phenoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 28 step (ii) as a yellow foam.
MS: FAB(-ve): 783(M-1)

(iv) 5-((4-Phenoxy)phenylmethyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 30 step (i) as a yellow solid.

MS: FAB(+ve): 443(M+1)

- 5 (v) The trisodium salt of 5-((4-phenoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester was prepared from the product of step (iv) according to the method of Example 24 steps (ii) and (iii) as a yellow solid.

³¹P NMR: δ (D₂O): -8.0(d), -10.25(d), -21.5(t);

MS: ESI(-ve): m/e 695 (M-2Na+2H)

10

Example 46

Trisodium salt of 5-((3-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester.

- 15 (i) 5-(Hydroxy-((3-phenylmethoxy)phenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using 3-phenylmethoxybenzaldehyde instead of benzophenone) as a colourless foam.

MS: FAB(-ve): 797(M-1)

20

- (ii) 5-((3-Phenylmethoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 30 step (i) as a colourless foam.

MS: FAB(-ve): 781(M-1)

25

- (iii) 5-((3-Phenylmethoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 28 step (ii) as a yellow foam.

MS: FAB(-ve): 797(M-1)

30

- (iv) 5-((3-Phenylmethoxy)phenylmethyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 44 step (iv) as a yellow solid.

MS: ESI: 457(M+1)

(v) The trisodium salt of 5-((3-henylmethoxy)phenylmethyl)-4-thiouridine 5' - (tetrahydrogen triphosphate) -P³ - monomethyl ester was prepared from the product of step (iv) according to the method of Example 24 steps (ii) and (iii) as a yellow solid.

³¹P NMR: δ (D₂O): -8.12(d), -10.33(d), -21.55(t);

5 MS: FAB(+ve): 777(M+1)

Example 47

Trisodium salt of 5-((4-phenylmethoxy)phenylmethyl)-4-thiouridine-5' - (tetrahydrogen-triphosphate)-P³-monomethyl ester.

10

(i) 5-(Hydroxy-((4-phenylmethoxy)phenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2', 3', 5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using 4-phenylmethoxybenzaldehyde instead of benzophenone) as a colourless foam.

15 MS: FAB(+ve): 883(M+Rb)

(ii) 5-((4-Phenylmethoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 28 step (i) as a colourless foam.

20 MS: FAB(+ve): 769(M+1), 853(M+Rb)

(iii) 5-((4-Phenylmethoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 28 step (ii) as a yellow foam.

25 MS: FAB(-ve): 797(M-1)

(iv) 5-((4-Phenylmethoxy)phenylmethyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 30 step (ii) as a yellow solid.

MS: FAB(+ve): 457(M+1)

30

(v) The trisodium salt of 5-((4-Phenylmethoxy)phenylmethyl)-4-thiouridine 5' - (tetrahydrogen triphosphate) -P³ - monomethyl ester was prepared from the product of step (iv) according to the method of Example 24 steps (ii) and (iii) as a yellow solid.

³¹P NMR: δ (D₂O): -8.0(d), -10.15(d), -21.5(t);

35 MS: ESI(-ve): 709(M-2Na+2H)

Example 48

Trisodium salt of 5-(4-(1,1-dimethylethyl)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester.

- 5 (i) 5-((4-(1,1-Dimethylethyl)phenyl)hydroxymethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using 4-(1,1-dimethylethyl)benzaldehyde instead of benzophenone) as a colourless foam.
¹H NMR: δ (CDCl₃): 8.13(s, 1H), 7.44(s, 1H), 7.15-7.45(m, 4H), 5.84(d, 1H), 5.80(d, 1H),
10 5.5(d, 1H), 4.57(d, 1H), 4.10(m, 1H), 3.98(m, 2H), 3.73(m, 1H), 3.60(m, 1H), 3.17(d, 1H), 3.13(d, 1H), 1.23(s, 9H), 0.81(s, 9H), 0.76(s, 9H), -0.15-0.05(m, 18H).
- (ii) 5-(4-(1,1-Dimethylethyl)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to
15 the method of Example 30 step (i).
¹H NMR: δ (CDCl₃): 8.04(s, 1H), 7.3(s, 1H), 7.17(d, 2H), 7.04(d, 2H), 5.85(d, 1H), 4.03(m, 1H), 3.93(m, 2H), 3.73(dd, 1H), 3.6(dd, 1H), 3.51(d, 2H), 1.2(s, 9H), 0.8(m, 27H), -0.2-0.0(m, 18H)
- 20 (iii) 5-(4-(1,1-Dimethylethyl)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)-dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 28 step (ii).
¹H NMR: δ (CDCl₃): 9.38(s, 1H), 7.28(s, 1H), 7.19(d, 2H), 7.05(d, 2H), 5.79(d, 1H), 4.06(dd, 1H), 3.95(m, 2H), 3.86(d, 1H), 3.77(d, 1H), 3.73(dd, 1H), 3.58(dd, 1H), 1.2(s, 9H), 0.81(s, 9H), 0.78(s, 9H), -0.15-0.00(m, 18H).
25
- (iv) 5-(4-(1,1-Dimethylethyl)phenylmethyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 28 step (iii).
¹H NMR: δ (CDCl₃): 11.15(s, 1H), 7.35(s, 1H), 7.16(s, 1H), 7.15(d, 2H), 5.73(d, 1H),
30 4.65(bs, 1H), 4.23(m, 1H), 4.13(bs, 2H), 4.95-4.05(bs, 1H), 3.81(d, 1H), 3.74(d, 1H), 3.5(bs, 2H), 1.3(s, 9H).
- (v) The trisodium salt of 5-(4-(1,1-dimethylethyl)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester was prepared from the product of step
35 (iv) according to the method of Example 24 steps (ii) and (iii) as a yellow solid.
³¹P NMR: δ (D₂O): -8.3(d), -10.7(d), -21.76(t);

MS: ESI-loop: 659

Example 49

5 Sodium salt of 5-(4-(1,1-dimethylethyl)phenylmethyl)-4-thiouridine-5'-(dihydrogen-phosphate) monomethyl ester

Obtained from the products of Example 48 step (v) by reverse phase HPLC purification of the final reaction mixture as a yellow solid using 10-50% methanol in 1% aqueous ammonium acetate solution.

10 ^{31}P NMR: δ (D_2O): 3.077(s)

MS: FAB(+ve): 523(M+1)

Example 50

15 Trisodium salt of 5-((3-methoxy-4-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)- P^3 -monomethyl ester.

(i) 5-(Hydroxy-((3-methoxy-4-phenylmethoxy)phenyl)methyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from 2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine according to the method of Example 1 step (i) (using 3-methoxy-4-phenylmethoxybenzaldehyde instead of benzophenone) as a colourless foam.

20 ^1H NMR: δ (CDCl_3): 8.3(bs, 1H), 7.2-7.45(m, 6H), 6.94(bs, 1H), 6.80(m, 2H), 5.85(2d), 5.45(d, 1H), 5.07(s, 2H), 4.03(m, 1H), 3.93(m, 2H), 3.8(s, 3H), 3.68(m, 1H), 3.58(m, 1H), 3.24(d, 1H), 0.82(s, 9H), 0.81(s, 9H), 0.76(s, 9H), -0.15-0.0(m, 18H).

25 (ii) 5-((3-Methoxy-4-phenylmethoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)uridine was prepared from the product of step (i) according to the method of Example 28 step (i).

30 ^1H NMR: δ (CDCl_3): 8.27(bs, 1H), 7.2-7.45(m, 6H), 6.71(s, 1H), 6.67(d, 1H), 6.54(dd, 1H), 5.86(d, 1H), 5.02(s, 2H), 4.03(m, 1H), 3.98(m, 2H), 3.76(s, 3H), 3.71(dd, 1H), 3.64(dd, 1H), 3.46(d, 1H), 3.51(d, 1H), 0.82(s, 9H), 0.81(s, 9H), 0.75(s, 9H), -0.2-0.0(m, 18H)

(iii) 5-((3-Methoxy-4-phenylmethoxy)phenylmethyl)-2',3',5'-tris-O-((1,1-dimethylethyl)dimethylsilyl)-4-thiouridine was prepared from the product of step (ii) according to the method of Example 28 step (ii).

35 ^1H NMR: δ (CDCl_3): 9.31 (s, 1H), 7.36(d, 2H), 7.35-7.25(m, 3H), 7.23(d, 1H), 6.76(d, 1H), 6.7(d, 1H), 6.54(dd, 1H), 5.83(d, 1H), 5.05(s, 1H), 4.08(m, 1H), 3.98(m, 2H), 3.79(s, 3H),

3.78(m, 1H), 3.71(dd, 1H), 3.6(dd, 1H), 0.84(s, 9H), 0.83(s, 9H), 0.79(s, 9H), -0.2-0.05(m, 18H)

- (iv) 5-((3-Methoxy-4-phenylmethoxy)phenylmethyl)-4-thiouridine was prepared from the product of step (iii) according to the method of Example 28 step (iii).

¹H NMR: δ (CDCl₃): 11.09(s, 1H), 7.25-7.5(m, 5H), 7.14(s, 1H), 6.72-6.68(m, 2H), 6.65(d, 1H), 5.66(d, 1H), 5.07(s, 2H), 4.67(bs, 1H), 4.23(m, 1H), 4.10(m, 2H), 4.00(s, 1H), 3.81(s, 3H), 3.70(m, 2H), 3.5(m, 2H)

- (v) The trisodium salt of 5-((3-methoxy-4-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester was prepared from the product of step (iv) according to the method of Example 24 steps (ii) and (iii) as a yellow solid.

³¹P NMR: δ (D₂O): -8.24(d), -10.45(d), -21.7(t);

MS: FAB(+ve): 807(M+1)

Example 51

Disodium salt of 5-((3-methoxy-4-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-(trihydrogen-diphosphate)-P²-monomethyl ester

- Prepared from the products of Example 50 step (v) by reverse phase HPLC purification using 10-50% methanol in 1% aqueous ammonium acetate solution followed by anion exchange chromatography (using Dowex-50 Na⁺ form) and lyophilisation of the aqueous solution obtained to secure a yellow solid.

³¹P NMR: δ (D₂O): -8.15(d), -10.2(d)

- ¹H NMR: δ (D₂O): 7.74(s, 1H), 7.4-7.2(m, 5H), 6.88(s, 1H), 6.78(d, 1H), 6.68(d, 1H), 5.77(d, 1H), 4.94(s, 2H), 4.25(m, 2H), 4.18(m, 1H), 4.10(m, 2H), 3.83(d, 1H), 3.73(d, 1H), 3.69(s, 3H), 3.41 (d, 3H).

Pharmacological Data

Example A

- The following example describes the assay used to determine how strongly the compounds of the invention bind to P2-purinoreceptor 7-TM G-protein coupled receptors. The assay used a human P2Y2 receptor clone which was isolated from HL60 cells cDNA and then stably transfected into a Jurkat cell line (using methods described in "Cloning and Characterisation of a Bovine P₂Y Receptor" Henderson *et al* (1995), 212, 2, 648-656; Parr *et al* Proc. Natl. Acad. Sci USA (1994), 91, 3275-3279 and Proc Natl Acad Sci USA

(1994), 91, 13067). The cloned receptor mediates an increase in intracellular calcium in the cell line, which possesses no endogenous nucleotide receptor of its own.

The transfected Jurkat cells were maintained at a concentration of from about 1×10^5 to 10×10^5 cells/ml in RPMI containing 4% heat inactivated bovine serum, 2% penicillin/streptomycin and 1% glutamine. The cells were incubated at 37°C in an atmosphere of air with 5% CO₂.

The cells were spun down at 1000 r.p.m. for 5 minutes and resuspended in 10ml basal salt solution (BSS) containing 125 mM of NaCl, 5 mM of KCl, 1 mM of MgCl, 1.5 mM of CaCl₂, 25 mM of HEPES, 5 mM of glucose and 1 mg/ml of bovine serum albumin, having a pH of 7.3. The concentration of cells was determined using a Technicon cell counter. From 0.75×10^8 to 1×10^8 cells were spun down, resuspended to a concentration of 3.3×10^7 cells/ml in BSS and incubated with either 17 μM fluo-3AM or 17 μM Fura-2AM at 37°C for 35 minutes with vigorous shaking. The dye used was dependent upon the fluorescence and absorption properties of the compounds of the invention. In general for compounds of formula (I) wherein Q¹ represents a S atom, fluo-3AM was used and for compounds wherein Q¹ represents an O atom, either fluo-3AM or fura-2AM were used. The cells were again spun down and washed once with the same volume of BSS before being resuspended in BSS to a concentration of 1×10^6 cells/ml ready for testing.

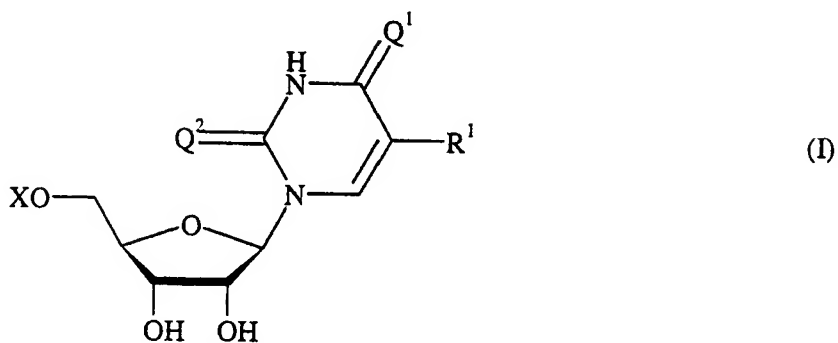
When fluo-3AM was used as the dye, the cell solution was left at room temperature to recover for approximately 30 minutes before testing. Fura-2AM loaded cells were divided into aliquots of about 10 ml and were warmed to 37°C for 10 minutes before testing.

Calcium responses were measured on a SPEX Fluomax using 508 nm excitation and 525 nm emission wavelengths at room temperature for Fluo-3AM loaded cells and 340/380 nm excitation and 510 nm emission wavelengths for Fura-2AM loaded cells. Each cuvette contained 2 ml of cells and was stirred at high speed throughout the test. Basal fluorescence was measured for 5 seconds before 20 μl of a 10^{-2} - 10^{-6} M solution of the test compound in water was added to the 2ml solution of the cells. The response was calibrated by the addition of Triton-X-100 (68 μl, 10% solution) and then EGTA (180 μl, 0.5 M solution). For each compound the response was compared to that of UTP.

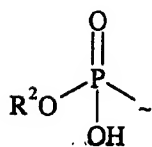
The compounds exemplified have pA₂ values greater than 4.0.

Claims

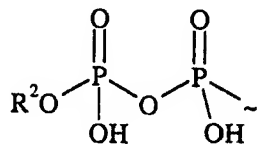
1. A compound of formula (I) or salts thereof:



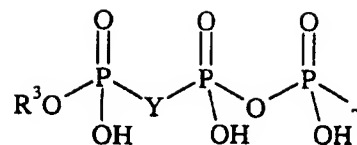
wherein X represents H or a group of formula (i), (ii) or (iii):



(i)

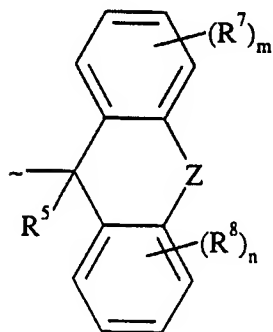


(ii)

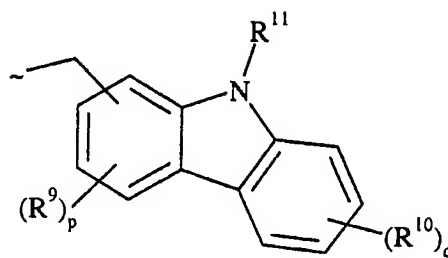


(iii)

R^1 represents a C_{1-6} -alkyl, $C(R^4)_2R^5$, CHR^6R^5 , $Si(R^4)_3$, $C(O)R^6$, or SR^6 group or
 R^1 represents a group of formula (iv) or (v):



(iv)



(v)

R^2 represents a hydrogen atom or methyl;

R^3 represents a hydrogen atom or a C_{1-6} -alkyl group which is optionally substituted by one or more C_{1-6} -alkoxy, C_{1-6} -alkylthio, C_{3-8} -cycloalkyl, and/or phenyl groups (wherein the

one or more phenyl groups are optionally substituted by one or more halogen atoms and/or hydroxy, C₁₋₄-alkyl and/or C₁₋₄-alkoxy groups);

R⁴ represents phenyl optionally substituted by one or more halogen atoms and/or one or more C₁₋₄-alkoxy, C₁₋₄-alkylthio and/or C₁₋₄-alkyl groups (wherein the one or more alkyl groups are optionally substituted by one or more F atoms);

R⁵ represents a hydrogen atom or a C₁₋₆-alkoxy, C₁₋₆-alkylthio, C₁₋₆-alkyl or a phenyl group;

R⁶ represents a C₆₋₁₀-aryl group which is optionally substituted by one or more halogen atoms and/or one or more C₆₋₁₀-aryl, C₆₋₁₀-aryloxy, C₆₋₁₀-arylthio, C₃₋₈-cycloalkyl,

C₁₋₆-alkylthio, C₁₋₆-alkyl and/or C₁₋₆-alkoxy groups, each of which substituents are optionally substituted by one or more halogen atoms and/or one or more C₁₋₆-alkyl, phenyl and/or C₁₋₆-alkoxy groups;

R⁷ and R⁸ each independently represent a halogen atom or a C₁₋₄-alkoxy, C₁₋₄-alkylthio or C₁₋₄-alkyl group (wherein the one or more alkyl groups are optionally substituted by one or more F atoms);

R⁹ and R¹⁰ each independently represent a halogen atom or a C₁₋₄-alkoxy, C₁₋₄-alkylthio, C₁₋₄-alkyl (optionally substituted by a phenyl group) or a C₃₋₈-cycloalkyl group;

R¹¹ represents C₁₋₆-alkyl group optionally substituted by phenyl;

Q¹ and Q² each independently represent O or S;

Y represents O or a CF₂, CCl₂ or a CBr₂ moiety;

Z represents a direct bond, O, S, (CH₂)_t (wherein when t is greater than 1, one of the CH₂ moieties is optionally replaced by an O or S atom), CH₂CH=CH, CH₂CH=CHCH₂ or CH=CH;

n, m, p and q each independently represent 0 or an integer from 1 to 4;

t represents an integer from 1 to 4;

• provided that:

(a) when X represents H then Q¹ represents a S atom and R¹ represents a group of formula (iv) where R⁵ is hydrogen, and Z is CH₂CH₂ or CH=CH;

(b) when R³ represents H then Y does not represent O;

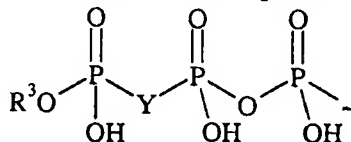
(c) when X represents a group of formula (i) or (ii) then:

(i) R¹ represents a group of formula (iv) wherein Z represents a direct bond, O, CH=CH, or CH₂CH₂, and R⁷, R⁸, n and m are as defined above; or

(ii) R¹ represents C(R⁴)₂R⁵ wherein R⁴ represents phenyl substituted by one or more halogen atoms and/or one or more C₁₋₄-alkoxy, C₁₋₄-alkylthio and/or C₁₋₄-alkyl groups

- (wherein the one or more alkyl groups are optionally substituted by one or more F atoms) and R^5 represents a hydrogen atom; or
- (iii) R^1 represents CHR^6R^5 wherein R^6 represents a C_{6-10} -aryl group which is substituted by one or more halogen atoms and/or one or more C_{6-10} -aryl, C_{6-10} -aryloxy, C_{6-10} -arylthio, C_{3-8} -cycloalkyl, C_{1-6} -alkylthio, C_{1-6} -alkyl and/or C_{1-6} -alkoxy groups, each of which optional substituents are optionally substituted by one or more halogen atoms and/or one or more C_{1-6} -alkyl, phenyl and/or C_{1-6} -alkoxy groups and R^5 is as defined above but does not represent phenyl;
- (d) when R^1 represents C_{1-6} -alkyl then Q^1 represents a S atom;
- (e) when R^1 represents CHR^5R^6 then R^5 does not represent phenyl.

2. A compound according to claim 1 wherein X represents



wherein R^3 and Y are as defined in claim 1.

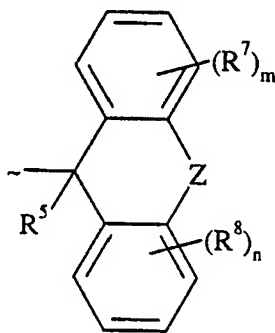
15

3. A compound according to claim 2 wherein Y represents CF_2 , CCl_2 , or CBr_2 , and R^3 represents hydrogen.

4. A compound according to any one of claims 1 to 3 wherein R^1 represents $C(R^4)_2R^5$ where R^4 represents phenyl substituted by one or more halogen atoms and one or more methyl groups and R^5 is hydrogen.

20

5. A compound according to any one of claims 1 to 4 wherein R^1 represents



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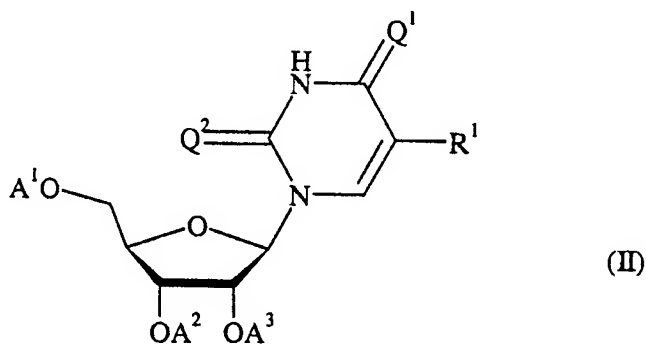
wherein R^7 and R^8 are hydrogen and Z is O, $(CH_2)_2$ or $CH=CH$.

6. A compound according to any one of claims 1 to 5 wherein Q^1 represents a S atom.
7. A compound according to claim 1 which is:
- monoanhydride of 5-diphenylmethyluridine-5'-phosphate with
- 5 dichloromethylenebisphosphonic acid;
- monoanhydride of 5-(9H-fluoren-9-yl)-4-thiouridine-5'-phosphate with
- dichloromethylenebisphosphonic acid;
- monoanhydride of 5-(9H-xanthen-9-yl)-4-thiouridine-5'-phosphate with
- dichloromethylenebisphosphonic acid;
- 10 monoanhydride of 5-(5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine-5'-phosphate with
- dichloromethylenebisphosphonic acid;
- 5-(5H-Dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine;
- monoanhydride of 5-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine-5'-
- phosphate with dichloromethylenebisphosphonic acid;
- 15 5-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-4-thiouridine;
- monoanhydride of 5-(1,1-bis(4-methylphenyl)methyl)-4-thiouridine-5'-phosphate with
- dichloromethylenebisphosphonic acid;
- monoanhydride of 5-(1,1-bis(4-chlorophenyl)methyl)-4-thiouridine-5'-phosphate with
- dichloromethylenebisphosphonic acid;
- 20 monoanhydride of 5-(1,1-bis(3,4-dichlorophenyl)methyl)-4-thiouridine-5'-phosphate with
- dichloromethylenebisphosphonic acid;
- monoanhydride of 5-(1,1-bis(4-methoxyphenyl)methyl)-4-thiouridine-5'-phosphate with
- dichloromethylenebisphosphonic acid;
- monoanhydride of 5-(3,6-dimethoxy-9H-fluoren-9-yl)-4-thiouridine-5'-phosphate with
- 25 dichloromethylenebisphosphonic acid;
- monoanhydride of 5-(3-(4-methylphenoxy)phenylmethyl)-4-thiouridine-5'-phosphate with
- dichloromethylenebisphosphonic acid;
- monohydride of 5-(3-(4-chlorophenoxy)phenylmethyl)-4-thiouridine-5'-phosphate with
- dichloromethylenebisphosphonic acid;
- 30 monoanhydride of 5-(3-(3,4-dichlorophenoxy)phenylmethyl)-4-thiouridine-5'-phosphate
- with dichloromethylenebisphosphonic acid;
- monoanhydride of 5-(3-(4-methoxyphenoxy)phenylmethyl)-4-thiouridine-5'-phosphate
- with dichloromethylenebisphosphonic acid;
- monoanhydride of 5-((3-methoxy-4-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-
- 35 phosphate with dichloromethylenebisphosphonic acid;

- monoanhydride of 5-((4-methoxy-3-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid;
- monoanhydride of 5-(4-butoxyphenylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid;
- 5 monoanhydride of 5-(9-ethylcarbazol-3-ylmethyl)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid;
- monoanhydride of 5-((4-phenyl)phenylthio)-4-thiouridine-5'-phosphate with dichloromethylenebisphosphonic acid;
- monoanhydride of 5-(9-methoxyfluoren-9-yl)uridine-5'-phosphate with
- 10 dichloromethylenebisphosphonic acid;
- monoanhydride of 5-((4-phenyl)phenylcarbonyl)uridine-5'-phosphate, monoanhydride with dichloromethylenebisphosphonic acid;
- 5-diphenylmethyluridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 5-diphenylmethyluridine-5'-(tetrahydrogen-triphosphate)-P³-mono(n-propyl) ester;
- 15 5-diphenylmethyluridine-5'-(tetrahydrogen-triphosphate)-P³-mono(2-methoxyethyl) ester;
- 5-diphenylmethyluridine-5'-(tetrahydrogen-triphosphate)-P³-monophenylmethyl ester;
- 5-diphenylmethyl-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 5-(1,1-bis(4-methoxyphenyl)methyl)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 20 5-(1,1-bis(4-methoxyphenyl)methyl)-4-thiouridine-5'-(tetrahydrogen triphosphate)-P³-monomethyl ester;
- 5-(1,1-bis(4-methoxyphenyl)methyl)-4-thiouridine-5'-(dihydrogen-phosphate)-monomethyl ester;
- 5-(9H-fluoren-9-yl)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 25 5-(9H-fluoren-9-yl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 5-(9H-fluoren-9-yl)-4-thiouridine 5'-(trihydrogen-diphosphate)-P³-monomethyl ester;
- 5-(9H-fluoren-9-yl)-4-thiouridine-5'-(dihydrogen-phosphate)-monomethyl ester;
- 5-triphenylsilyluridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 5-phenylthiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 30 5-ethyl-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 5-((4-methoxy)phenylthio)uridine-5'-(tetrahydrogen triphosphate)-P³-monomethyl ester;
- 5-((2-phenyl)phenylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 5-((3-phenyl)phenylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 5-((4-phenyl)phenylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
- 35 5-(2-naphthylthio)uridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;

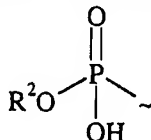
- 5-((3-phenoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
 5-((4-phenoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
 5-((3-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
 5-((4-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
 5-(4-(1,1-dimethylethyl)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester;
 5-(4-(1,1-dimethylethyl)phenylmethyl)-4-thiouridine-5'-(dihydrogen-phosphate)-monomethyl ester;
 5-((3-methoxy-4-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-(tetrahydrogen-triphosphate)-P³-monomethyl ester; or
 5-((3-methoxy-4-phenylmethoxy)phenylmethyl)-4-thiouridine-5'-(trihydrogen-diphosphate)-P²-monomethyl ester;
 or pharmaceutically acceptable salts thereof.

8. A process for preparing a compound according to claim 1 which comprises:
 (a) for a compound of formula (I) wherein X represents H, deprotecting a compound of formula

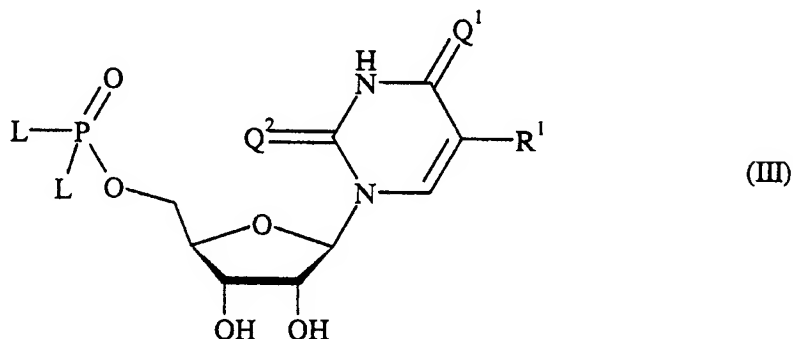


wherein R¹, Q¹ and Q² are as defined in claim 1 and A¹, A² and A³ each independently represent a protecting group;

- (b) for a compound of formula (I) wherein X represents

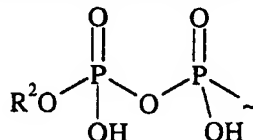


wherein R^2 is as defined in claim 1, reacting the product of step (a) with a phosphorylating agent $P(O)L_3$ wherein each L is the same or different and represents a leaving group, to yield an intermediate of formula



- 5 wherein L is as defined above and Q^1 , Q^2 and R^1 are as defined in claim 1, and either hydrolysing the intermediate of formula (III) thus obtained under alkaline conditions or reacting it with MeOH followed by alkaline hydrolysis;

(c) for a compound of formula (I) wherein X represents

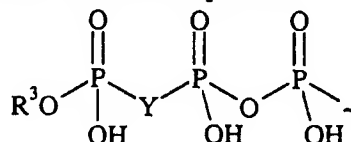


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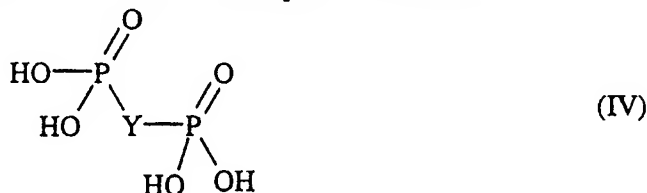
wherein R^2 is as defined in claim 1, hydrolysing an intermediate of formula (III) as defined above and then reacting it with a phosphorylating agent $P(O)L_3$ as defined above, and either hydrolysing the product under alkaline conditions or reacting it with MeOH followed by alkaline hydrolysis;

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(d) for a compound of formula (I) wherein X represents



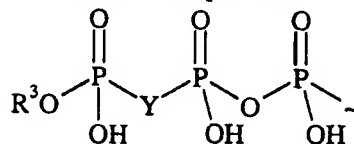
wherein R^3 represents H and Y is as defined in claim 1, reacting an intermediate of formula (III) as defined above with a salt of a compound of formula



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wherein Y is as defined in claim 1 followed by alkaline hydrolysis; or

(e) for a compound of formula (I) wherein X represents



wherein R^3 is as defined in claim 1 but does not represent H and Y is as defined in claim 1,
 5 reacting the product of step (d) with a phosphorylating agent $P(O)L_3$ as defined above, and
 reacting the product with R^3OH wherein R^3 is as defined above; and, optionally thereafter
 any of the above processes forming a salt.

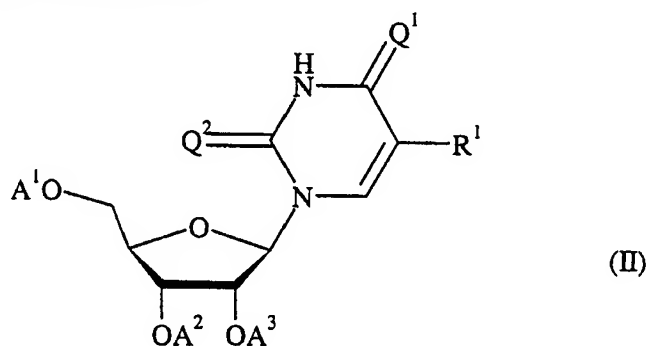
9. A compound according to any one of claims 1 to 7 for use in therapy.

10. A pharmaceutical composition which comprises a compound according to any one of
 claims 1 to 7 in association with a pharmaceutically acceptable excipient and/or adjuvant.

11. A method of medical treatment which comprises administering to a patient suffering
 15 from an inflammatory condition a therapeutically effective amount of a compound
 according to any one of claims 1 to 7.

12. Use of a compound according to any one of claims 1 to 7 in the manufacture of a
 medicament for use in the treatment of an inflammatory condition.

13. An intermediate of formula (II):



wherein A^1 , A^2 and A^3 each independently represent a protecting group and Q^1 , Q^2 and R^1
 are as defined in claim 1 provided that R^1 does not represent C_{1-6} -alkyl or $C(O)R^6$,
 25 CHR^5R^6 or SR^6 when R^6 represents unsubstituted phenyl and R^5 is as defined in claim 1
 but does not represent a H atom.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00587

A. CLASSIFICATION OF SUBJECT MATTER		
IPC6: C07H 19/06, C07H 19/067, C07H 19/10 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC6: C07H		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CA, WPI		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 3048877 A1 (GAURI, KAILASH KUMAR), 8 July 1982 (08.07.82) --	1-10,12-13
A	WO 8400759 A (SANDOZ-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H.), 1 March 1984 (01.03.84) --	1-10,12-13
A	GB 1193531 A (THE UPJOHN COMPANY), 3 June 1970 (03.06.70) --	1-10,12-13
A	DE 3048873 A1 (ROBUGEN GMBH), 15 July 1982 (15.07.82) --	1-10,12-13
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
2 July 1998		06 -07- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer Eva Johansson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00587

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chem.Pharm.Bull., Volume 18, No 2, 1970, Masako Muraoka et al, "Alkylated Pyrimidine Derivatives as Antiviral Agents. I. Synthesis and Antiviral Screening of Alkylpyrimidine and 5-Alkyluracil Nucleoside" --	1-10,12-13
A	WO 9413687 A1 (PRO-NEURON, INC.), 23 June 1994 (23.06.94) -- -----	1-10,12-13

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00587

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

09/06/98

International application No.

PCT/SE 98/00587

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
DE	3048877	A1	08/07/82	NONE	
WO	8400759	A	01/03/84	AU 1800483 A BE 897516 A DE 3390162 T DK 372283 A FI 832884 A FR 2531962 A,B GB 2125401 A,B JP 59053499 A NL 8302859 A PT 77209 B SE 8304408 A	23/02/84 13/02/84 21/02/85 18/02/84 18/02/84 24/02/84 07/03/84 28/03/84 16/03/84 18/03/86 18/02/84
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DE	3048873	A1	15/07/82	NONE	
WO	9413687	A1	23/06/94	AU 5730594 A CA 2150940 A CN 1095268 A EP 0679160 A IL 107900 D JP 8503699 T MX 9307765 A US 5691320 A ZA 9309208 A	04/07/94 23/06/94 23/11/94 02/11/95 00/00/00 23/04/96 30/06/94 25/11/97 08/08/94